NOVARTIS

Novartis Research and Development

Ruxolitinib (INC424), siremadlin (HDM201), crizanlizumab (SEG101), sabatolimab (MBG453), rineterkib (LTT462), NIS793

Clinical Trial Protocol CINC424H12201 / NCT04097821

A randomized, open-label, phase I/II open platform study evaluating safety and efficacy of novel ruxolitinib combinations in myelofibrosis patients

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Ab	antibody
ADR	adverse drug reactions
AE	adverse event
AF	atrial fibrillation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASCT	allogeneic hematopoietic stem cell transplantation
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUC	Area under curve
BID	twice a day
BLRM	Bayesian logistic regression model
BM	bone marrow
C1D1	Cycle 1 Day 1 (and sequentially for other cycles and days, eg C1D2, C2D1 etc.)
CFR	Code of Federal Regulation
COVID-19	coronavirus disease 2019
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRS	Cytokine Release Syndrome
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome P-450
DDI	Drug-drug interaction
DDS	Dose-Determining Set
DILI	Drug-Induced Liver Injury
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DOACs	Direct oral anticoagulants
DUSP6	Dual specificity phosphatase 6
DVT	Deep vein thrombosis
EC	Ethics committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOI	End of infusion
EORTC	European Organization for Research and Treatment of Cancer

EOS	End of study
EOT	End of treatment
ePRO	electronic patient reported outcome
ERK	Extracellular signal-regulated kinase
ESA	Erythropoiesis-stimulating agents
ESMO	European Society for Medical Oncology
ET	essential thrombocythemia
EWOC	escalation with overdose control
FDA	Food and Drug Administration
G-CSF	Granulocyte-Colony Stimulating Factor
GCP	Good Clinical Practice
GDF15	Growth Differentiation Factor 15
GLDH	Glutamate Dehydrogenase
GLP	Good Laboratory Practice
GGT	gamma-glutamyl-transferase
GvHD	Graft versus Host Disease
Hb	hemoglobin
HBV	Hepatitis B
HCV	Hepatitis C
HDM2	Human Double Minute-2
HEV	Hepatitis E
HIV	human immunodeficiency virus
HSC	hematopoietic stem cell
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IG	immunogenicity
INR	International normalized ratio
irAE	Immune-Related Adverse Events
IRB	Institutional Review Board
IRR	Infusion-related reactions
IRT	Interactive Response Technology
IV	Intravenous
IWG-MRT	International Working Group-Myeloproliferative Neoplasms Research and Treatment
JAK	Janus kinase
LCM	left costal margin
LFT	Liver function test
LLN	lower limit of normal
LLOQ	lower limit of quantification
LMWH	low molecular weight heparin
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MAP	meta-analytic-predictive
MAPK	Mitogen-activated protein kinase
MDS	Myelodysplastic syndrome

MedDRA	Medical dictionary for regulatory activities
MEK	Mitogen-activated protein kinase kinase
MF	myelofibrosis
MFSAF	Myelofibrosis Symptom Assessment Form
MK	megakaryocyte
mPDAC	Metastatic pancreatic ductal adenocarcinoma
MPN	myeloproliferative neoplasm
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCCN	National Comprehensive Cancer Network
NGS	next generation sequencing
NK	Natural Killer
NTproBNP	N-terminal pro b-type natriuetic peptide
OATP	organic-anion-transporting polypeptide
PD	pharmacodynamic(s)
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PET-MF	post-essential thrombocythemia myelofibrosis
PFS	progression free survival
[redacted]	[redacted]
PK	pharmacokinetic(s)
PLT	platelets
PMF	primary myelofibrosis
PML	progressive multifocal leuko-encephalopathy
PO	Oral
PPV-MF	post-polycythemia vera myelofibrosis
PRBC	packed red blood cells
PRO	patient reported outcome
PSDS	post-study drug supply
PTA	Post-Trial Access
PtdSer	phosphatidylserine
PV	polycythemia vera
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
QD	once a day
QLQ-C30	Quality of Life Questionnaire-Core 30
QoL	quality of life
RBC	red blood cell(s)
REB	Research Ethics Board
RP2D	recommended phase 2 dose
RR	Response rate
R/R	relapsed/refractory
RVO	retinal vein occlusion

SAE	serious adverse event
SAF	symptom assessment form
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	Steering Committee
SCD	sickle cell disease
sCR	serum creatinine
SD	standard deviation
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
SOC	Standard of care
STAT	signal transducer and activator of transcription
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEN	toxic epidermal necrolysis
TBC	to be confirmed
TBIL	Total bilirubin
TFQ	Trial Feedback Questionnaire
TGFβ	transforming growth factor beta
TIM-3	T Cell Immunoglobulin Mucin 3
TLS	Tumor lysis syndrome
TNF-α	Tumor necrosis factor alpha
TReg	Regulatory T cells
TSS	total symptom score
ULN	upper limit of normal
USA	United States of America
VOC	vaso-occlusive crises
WHO	World Health Organization
WOCBP	Women of child-bearing potential
YBX1	Y-box binding protein 1

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product”.
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Part	A single component of a study which contains different objectives or populations within that single study.
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	An individual who has consented to participate in this study
Subject number	A number assigned to each subject who enrolls in the study. When combined with the center number, a unique identifier is created for each subject in the study.
Withdrawal of study consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Amendment 9 (05-Dec-2023)

Amendment rationale

The main purpose of this amendment is to increase the duration of the extension treatment phase for the remaining patients to a maximum of 21 cycles. The enrollment remains halted as per protocol amendment 08.

Changes to the protocol

The following changes are implemented:

- Update to the study design to increase the duration of the extension phase from 12 cycles to 21 cycles.
- Updates to the investigational treatments (Table 6-1). Only the investigational drug strengths intended to be used during the extension phase, with ongoing patients receiving treatment, will be submitted to Health Authorities (i.e. ruxolitinib, siremadlin, rineterkib) as applicable, unless otherwise required from a local regulatory compliance perspective in any participating country. Siremadlin 40 mg is not applicable as it will no longer be investigated due to enrollment halt, and there are no ongoing subjects receiving such drug strength.
- Updates to the study assessment to reduce the burden for ongoing subjects.
- Updates in protocol summary related to the amendment 09.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Figure 3-1 and Figure 3-2: Planned duration of extension treatment phase have been updated to reflect the addition of 9 cycles.
- Section 4.1: The extension treatment phase has been updated to reflect the addition of 9 cycles.
- Section 6.1.5: The extension treatment phase has been updated to reflect the addition of 9 cycles.
- Section 6.6.1: The availability of a patient diary for oral treatment compliance has been removed.
- Table 6-1: Investigational drugs has been updated to indicate that siremadlin (HDM201) 40 mg is not applicable.
- Table 8-2: The study assessments of coagulation, urinalysis, and thyroid function have been removed from Cycle 2 and subsequent cycles in the extension treatment phase to reduce the burden for ongoing subjects.
- Section 9.2: Study completion has been updated to reflect the addition of 9 cycles of the extension treatment phase.
- Section 10.1.2: Definition and recording of Hy's Law has been added to ensure compliance with FDA request for expedited reporting of potential Hy’s Law cases.
- Section 12: Data analysis has been updated to reflect the addition of 9 cycles of the extension treatment phase.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 8 (05-Oct-2022)

Amendment rationale

The main purpose of this amendment is to reflect the changes in study conduct which are a result of the permanent enrollment halt decision by Novartis. These changes include adding an extension treatment phase and reduction of study assessments to decrease subject's burden in Part 1.

At the time of this amendment:

- 46 subjects have been enrolled in the study in Part 1 and Part 2 with the last patient first visit occurring on 15-Jun-2022.
- As of the 05-Oct-2022, 4 subjects are ongoing in Part 1. Four subjects are receiving treatment in the ruxolitinib+siremadlin and ruxolitinib+rineterkib arms and all of them have completed at least six treatment cycles. 3 subjects are in the safety follow-up period (1 subject in the 30 days after last dose in the ruxolitinib+siremadlin arm and, 2 subjects in the 30 and 90 days after last dose in the ruxolitinib+NIS793 arm).
- No subject is ongoing in Part 2, and Part 3 will not be initiated.
- Recruitment of subjects has been halted since 17-Jun-2022.

Due to the rapidly evolving competitive landscape in drug development for myelofibrosis, with multiple ongoing trials and continued challenges with recruitment, Novartis decided to discontinue the development program for INC424H1. Therefore the CINC424H12201 study recruitment was terminated. This decision was not triggered by any patient safety signals or measures.

Novartis is committed to providing access to the investigational drug combination when a subject is benefitting from the treatment. Therefore, this amendment defines a core treatment phase and introduces an extension treatment phase in Part 1 to provide study treatment until the subject no longer derives clinical benefit, meets one of the defined discontinuation criteria or until subject completes extension treatment phase, whichever occurs first.

In consideration of the enrollment halt, a number of preplanned study objectives will not be pursued. Following the communication of permanent enrollment halt, investigators were instructed to halt unnecessary study procedures, such as pharmacokinetics (PK) [redacted], to reduce the burden for ongoing subjects. This will be summarized in the clinical study report.

Changes to the protocol

The following changes are implemented:

- Update to the study design to define the core treatment phase for Part 1 and introduce the extension treatment phase for Part 1 subjects (after completion of the core treatment phase). The extension treatment phase is not applicable for Parts 2 and 3 as no subject is ongoing in these parts at the time of this amendment.
- Addition of inclusion and exclusion criteria for the extension treatment phase.

- Addition of objectives and endpoints, to evaluate safety and tolerability during the extension treatment phase (Table 2-1) and the corresponding visits and evaluations schedule (Table 8-1, Table 8-2).
- Updates to the investigational treatments (Table 6-1). Only the investigational drugs intended to be used during the extension phase, with ongoing patients receiving treatment, will be submitted to Health Authorities (i.e. ruxolitinib, siremadlin, rineterkib) as applicable, unless otherwise required from a local regulatory compliance perspective in any participating country.
- Updates to the definition and timing of the primary and final analyses.
- Updates in protocol summary related to the amendment 08 and updates in the list of abbreviations.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Section 1.1.2.1: Updated information about ruxolitinib and GvHD.
- Section 1.1.2.2: Updated information about siremadlin.
- Section 1.1.2.5: Updated information about rineterkib in combination therapy.
- Section 1.1.2.6: Updated information about NIS793 in combination therapy.
- Section 1.2: Definition of Part 1 includes now a core and extension treatment phase. The purpose of the extension treatment phase was added.
- Section 2: Objectives have been updated to reflect the enrollment halt and the addition of extension treatment phase
- Section 3: The study design has been adapted to include an extension treatment phase. Part 1 includes now as core and an extension treatment phase. Part 2 remains unchanged as the only randomized subject was discontinued. Part 3 is not applicable anymore. Study design figures have been updated.
- Section 4.1: The core treatment phase end and the extension treatment phase have been described in this section
- Section 4.2.6: This is a new section and it was added to describe the extension treatment phase.
- Section 4.4: Information about the applicability of Part 2 and Part 3 was added.
- Section 4.5: Enrollment halt rationale was added
- Section 5: Information about the applicability of Part 2 and Part 3 was added.
- Section 5.3: This is a new section included to describe the inclusion and exclusion criteria for the extension treatment phase.
- Section 6.1.1: Information about the applicability of investigational drugs was added. Investigational Drug supply for core and extension treatment phase specified.
- Section 6.1.3: The possibility for subjects in Part 1 to continue in an extension treatment phase was added. Information about the applicability of Part 2 and Part 3 was added.
- Section 6.1.5: The maximum treatment duration of the core and extension treatment phase is defined in this section. Information about the applicability of Part 2 and Part 3 was added.

- Section 6.2.1.1: Applicability of the section specified for the extension treatment phase.
- Section 6.2.1.1.2: Applicability of the section specified for the extension treatment phase.
- Section 6.2.1.1.3: Applicability of the section specified for the extension treatment phase.
- Section 6.2.2: The list of prohibited medication has been specified to the extension treatment phase as well. The information about fluconazole (prohibited medication) has been updated. Fendratinib added to the prohibited medications.
- Section 6.2.2.1 Applicability of the section specified for the extension treatment phase.
- Section 6.2.2.2 Applicability of the section specified for the extension treatment phase.
- Section 6.2.2.3 Applicability of the section specified for the extension treatment phase.
- [redacted]
- Section 6.5.4.1: Information about the applicability during the extension treatment phase was added.
- Section 6.5.5: Confirmation that the guidelines apply to extension treatment phase as well.
- Section 6.6: Information about the applicability during the extension treatment phase was added.
- Section 6.6.1: The availability of a patient diary for oral treatment compliance has been added.
- Section 7: Re-consent for patients entering the extension treatment phase has been added.
- Section 8: Revisions to text and visit schedule tables have been made to this section to include the core and extension treatment phase. Addition of the recommendation on cycle length for subjects on siremadlin combination. Information about the applicability of Part 2 and Part 3 was added. Allowable visit window table was updated. Appendix of Table 8-2 updated.
- Section 8.3: Information about the applicability of Part 2 and Part 3 was added.
- Section 8.3.2: Information on secondary endpoints added to Part 1 was added.
- Section 8.3.2.1: This section if not applicable anymore.
- Section 8.3.2.2: Assessment of spleen volume by MRI or CT scan when clinically indicated was added in the extension treatment phase.
- Section 8.3.2.4 Progression Free Survival is not applicable anymore.
- Section 8.3.2.5: This is a new section heading for disease progression.
- Section 8.3.2.6 This section if not applicable anymore.
- Section 8.3.3: Extension treatment phase efficacy assessment section was added.
- Section 8.4.2: Applicability of ECG assessments for core and extension phases has been added in the section and tables.
- Section 8.4.4: Cardiac imaging assessments for core and extension treatment have been added.
- Section 8.5.1: The applicability of COAs during the extension treatment phase is added. Table 8-18 and Table 8-23 were updated.

- Section 8.5.2: The collection of PK samples has been halted for the ongoing patients in the core treatment phase. No PK sample collection will be done during the extension treatment phase.
- Section 8.5.2.1: Applicability of sample collection is specified.
- [redacted]
- Section 9.1.1: Criteria for the discontinuation of patients in the extension treatment phase have been added.
- Section 9.2: Information about study completion has been updated.
- Section 10.2.1: Information about the applicability of Part 2 and Part 3 was added.
- Section 10.2.2: Information about the applicability of Part 2 and Part 3 was added.
- Section 12: Updates to specify the applicability of Part 2 and Part 3 data analysis has been made. Updates to the timing and the data to be included for both the primary analysis and the final analysis respectively.
- Section 12.4: Information about the applicability of Part 2 and Part 3 was added.
- Section 12.5: Information about the applicability of Part 2 and Part 3 was added.
- Section 12.5.1.2: Specified the core treatment phase and the extension treatment phase analyses for change in spleen size (length and volume).
- Section 12.5.1.3 Information about the applicability of EORTC QLQ-C30 in Part 1, Part 2 and Part 3 was added.
- Section 12.5.2: Defined ”on-extension treatment period” and clarified the analysis for the core treatment phase and the extension treatment phase safety endpoints.
- Section 12.5.3 Descriptive statistics paragraph has been updated.
- Section 12.5.3.2 and Section 12.5.4: Information about the applicability of immunogenicity [redacted] endpoints was added.
- [redacted]
- [redacted]
- Section 12.6.5 Information about the applicability during the extension treatment phase was added.
- [redacted]
- Section 12.7: Information about the applicability of interim analysis was added.
- Section 14.1: Impact of the enrollment halt on decision to reduce assessments is summarized.
- Appendix 16.7 and Appendix 16.8: Updated applicability of scenarios for Part 2 and Part 3.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. As a result of the permanent enrollment halt, a number of preplanned study objectives from the core treatment phase (Parts 1, 2, and 3) could not be pursued and investigators were instructed not to perform some of the planned procedures to reduce the burden on ongoing subjects in Part 1 prior to amended protocol version 08 approval. The assessments not performed in the core treatment phase because of the enrollment halt prior to protocol amendment's IRB/IEC approval will be documented for transparency in the clinical study report.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Local Protocol Amendment 7-US.01 (08-Apr-2022)

Amendment rationale

At the time of this amendment, 43 subjects have been enrolled in Part 1 of this study.

The main purpose of this local amendment for USA is to include additional strengths of ruxolitinib tablets beyond the strength of 5 mg currently allowed per study protocol version 07.

Considering that ruxolitinib will be supplied locally as commercially available for USA only, the purpose of this amendment is to allow the use of all available ruxolitinib strengths (per US FDA approved label) including 5 mg, 10 mg, 15 mg, 20 mg and 25 mg for US patients enrolling in the study.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

The following sections of the protocol have been changed:

- Section 6.1.1 Investigational and control drugs: Table 6-1 Investigational drugs: clarified that provision of ruxolinitib 5mg strength will be global and local for USA only, and updated to add new strengths (10 mg, 15 mg, 20 mg and 25 mg) of ruxolitinib for USA.
- Section 6.3.2 Treatment assignment, randomization: updated to clarify that no medication number will be provided for local supply of ruxolitinib in USA.
- Section 6.7.1.1 Handling of study treatment: clarified that medication number is not applicable for the local supply of ruxolitinib in USA.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein do NOT affect the Informed Consent.

Amendment 7 (11-Jan-2022)

Amendment rationale

At the time of the amendment, 38 subjects have received study treatment in this study in Part 1.

The purpose of this global amendment is to:

- Allow patients requiring packed red blood cell (PRBC) transfusions at any timepoint prior to first dose of study treatment to participate in all parts of the study (currently only eligible for Part 1 of the study). Nearly 40% of MF patients have hemoglobin (Hb) levels < 10 g/dL at diagnosis, and nearly one-quarter of MF patients at time of initial diagnosis already need red blood cell transfusions. The etiology of anemia in patients with myelofibrosis is multifactorial in origin, and the frequency with which patients who have myelofibrosis require PRBC transfusions varies. Restricting inclusion in Parts 2 and 3 (inclusion criteria#11) to *Subjects who do not require packed red blood cells (PRBC) transfusion at screening and will not require any PRBC transfusions within 4 weeks prior to first dose of study treatment* limits enrollment of patients who may require more frequent transfusions, and the timing of when transfusions are required may not be easy to predict. These patients would also potentially benefit from study treatment, and the current composite endpoint remains clinically relevant.

  Therefore, this inclusion criteria is being removed with this protocol amendment.

  This change is anticipated to primarily improve enrollment in Parts 2 and 3, and there is no impact on overall patient safety profile expected. The implementation of this change will allow a consistent patient population in Parts 2 and 3 as it is currently in Part 1.
- Add details on the endpoints definitions to assess the following secondary objectives (i) changes in symptoms of myelofibrosis using MFSAF v4.0 scale and (ii) changes in spleen volume to include pre-defined threshold of improvement to make the secondary efficacy evaluation endpoints more transparent.
- Add a new strength of rineterkib to allow additional doses of rineterkib to be tested if ever required.
- Updated exclusion criteria #17 to provide a more comprehensive guidance on the time gap between administration of monoclonal antibody or immunoglobulin-based agent for NIS793, crizanlizumab or sabatolimab arms (within 1 year) and rineterkib or siremadlin arms (within ≤4 weeks of screening or ≤5 half-lives whichever is shorter).
- [redacted]

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Protocol Summary has been updated with key changes.
- Section 1.1.2.1: Ruxolitinib background updated with the fact that it is now also approved for chronic GvHD in the USA.

- Section 2: Endpoints definitions for two secondary efficacy objectives were clarified as outlined under rationale.
- Section 3: Study design clarification of the condition to allow a subject to participate in more than one part of the study was added.
- Section 4.1: Clarification of the condition to allow a subject to participate in more than one part of the study was added.
- [redacted]
- Section 5: Inclusion and exclusion criteria were updated as follows:
  - To remove the inclusion 11 as outlined under rationale
  - To update the exclusion criteria 17 for respective compounds
  - To clarify that exclusion 25 restricts the use of platelet transfusion while PRBC is allowed.
- Section 6.1.1: Updated Table 6-1 to add a new strength of rineterkib.
- Section 6.2.1.1.2: Clarification that vaccination against COVID-19 is allowed unless these are attenuated vaccines but should not be administered on the day of the study treatment administration.
- Section 6.2.2: Clarification that all live vaccines are prohibited for all treatment arms was added as it was outlined already in the Section 6.2.1.1.2. Clarification of the alternative names of Hydroxyurea (Hydrea and Hydroxycarbamide) added.
- Section 6.2.2.2: Ruxolitinib single arm removed as it was listed by mistake. Monoclonal antibody is not a prohibited medication for ruxolitinib single agent.
- Section 6.5.4: [redacted]
- [redacted]
- Section 8: Table 8-3: the frequencies of the thyroid function and hepatitis test were updated to be consistent across all parts and all arms of the study.
- Section 8.2: Rationale for the collection of race and ethnicity when allowed by local authorities was added.
- Section 8.5.1: Clarification that TFQ is not considered study data and will be received electronically outside of the clinical database added.
- [redacted]
- Section 10.1.3: Terminology around SAE reporting time updated to say that if more stringent, local regulations regarding reporting timelines prevail.
- Section 12.5.1.2: Clarification added on the change in spleen length.

- Section 12.5.1.3: Clarification added on the change in symptoms assessed by MFSAF.
- Section 15: Additional reference has been added.
- In addition, clarifications and corrections were made throughout the protocol to improve consistency and understanding.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 6 (20-Jul-2021)

Amendment rationale

At the time of the amendment, 27 subjects have received study treatment in this study in Part 1.

The purpose of this global amendment is to:

- Update the eligibility criteria to reduce the time required for patients to be treated with ruxolitinib from "at least 24 weeks" to "at least 12 weeks" prior to first dose of study treatment, and also to reduce the time required for patients to be on a stable prescribed dose of ruxolitinib (no dose adjustments) prior to first dose of study treatment from "≥ 8 weeks" to "≥ 4 weeks". While this change is anticipated to primarily improve patient's enrolment, no impact on overall patient safety profile is expected. The implementation of this change at this stage of the study will allow a consistent patient population in the randomized Part2 and Part3.
- Provide more detailed guidance regarding dose modifications of siremadlin, rineterkib and NIS793 in case of toxicity including to allow patients to continue on study treatment at a reduced dose level for siremadlin or rineterkib or, at a reduced frequency for NIS793 if patients derive clinical benefits as per investigator's judgement.
- Additional precautionary measures have been implemented based on emerging new NIS793-related preclinical safety findings including update of exclusion criteria for impaired cardiac function, addition of cardiac imaging and cardiac enzymes safety assessments during treatment to enhance cardio-vascular mitigation as outlined in latest investigator brochure Edition 6.
- Additional guidance on dose discontinuation for NIS793 in case of Drug-induced liver injury (DILI).
- [redacted]
- Update the withdrawal of consent language as per the latest Novartis protocol template.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Protocol Summary has been updated with key changes.
- Study treatment LTT462 has been updated to rineterkib throughout the protocol including in Figure 3-1, Figure 3-2 and Figure 3-3.
- Section 1.1.2.6: Section was updated to include new NIS793 preclincial safety findings of vascular inflammation, tubulo-interstitial nephritis observed in non-clinical toxicology studies and cardiac valvulopathy in pharmacology study.

- [redacted]
- Section 3: Added the loading dose of crizanlizumab at C1D15 to the description of ruxolitinib +crizanlizumab arm in Part 1 and Part 2 for completeness.
- Section 4.1: Updated to reduce the time required for patients to be treated with ruxolitinib to "at least 12 weeks" and a stable dose for "at least 4 weeks" prior to first dose of study treatment.
- Section 4.3.4: Updated section to include preclinical evidence supporting the choice of Rineterkib as a treatment in patients with myelofibrosis for completeness.
- Section 4.3.6: Removed the rationale and reference to collection of bone marrow aspirate for megakaryocyte characterization.
- Section 4.5: Added rationale to monitor cardiac and renal functions for subjects receiving NIS793.
- Section 5: Updated the patient population to be patients treated with ruxolitinib for "at least 12 weeks" prior to first dose of study treatment, and for patients to be on a stable prescribed dose of ruxolitinib to "at least 4 weeks" prior to first dose of study treatment.
- Section 5.1: Inclusion criteria #5 has been updated to reduce the number of weeks required for patients to be treated with ruxolitinib from "at least 24 weeks" to "at least 12 weeks" prior to first dose of study treatment.
- Section 5.1: Inclusion criteria #6 has been updated to reduce the number of weeks required for patients to be on a stable prescribed dose of ruxolitinib (no dose adjustments) prior to first dose of study treatment from "≥ 8 weeks" to "≥ 4 weeks".
- Section 5.2: Exclusion Criteria #12 has been updated to further clarify cardiac exclusion criteria, including exclusion of patients who have had coronary stenting, or bypass surgery within 6 months. Additionally, for NIS793 arms in Part 1 and all arms in Parts 2 and 3 if NIS793 is open for enrollment, additional exclusion criteria have been added including Cardiac valvulopathy ≥ Grade 2, elevated cardiac enzymes (troponin I) elevation > x2 ULN, and medical history or current diagnosis of myocarditis.
- Section 5.2: Exclusion Criteria #13 has been updated to include uncontrolled atrial flutter / fibrillation as part of significant cardiac arrhythmias.
- Section 6.1.3: Added the loading dose of crizanlizumab at C1D15 to the description of ruxolitinib +crizanlizumab arm for completeness.
- Section 6.1.5: Added wording that ongoing patients will continue to receive study treatment in all parts as long as they derive benefits from the treatment to align with the other protocol sections that were updated in protocol amendment 2.
- Section 6.2.1: Reduced the requirement of prior ruxolitinib treatment to be recorded in the eCRF to "at least 12 weeks" prior to the first dose of study treatment, including the dosing information "up to 4 weeks" prior to study treatment.
- Section 6.5.1.1: Reduced the stable dose of ruxolitinib prior to first dose of study treatment to 4 weeks and clarified that the dose of ruxolitinib could be modified due to toxicity as outlined in Section 6.5.4.

- [redacted]
- Section 6.5.5.1: Updated the follow up for toxicity for siremadlin (Table 6-10) [redacted]
- Section 6.5.5.3: Table 6-11 and additional guidance on potential drug-induced liver injury (DILI) added.
- Section 6.6: Additional guidance and clarification added for the management of TLS.
- Section 8 Table 8.1: Visit windows for the different assessments and parts of the study were clarified. The window for cardiac imaging and ophthalmologic exams is -3 days for C1D1 visit in Part 2 and 3 of the study and was increased to -7 days for the Day 1 visit of all subsequent cycles in all parts.
- [redacted]
- Section 8: Updated assessment schedules in Tables 8-4 and 8-5 to reflect additional cardiac assessments for NIS793 arms, including ECG, cardiac imaging and cardiac enzyme assessments at baseline and during treatment cycles. Table 8-3 was also updated to include cardiac markers at screening for all treatment arms in Parts 2 and 3 if NIS793 is open for enrollment.
- Section 8.2: Updated the prior ruxolitinib treatment to "≥ 12 weeks" and on a stable dose "≥ 4 weeks". [redacted] the collection of Troponin I and NTproBNP and Cardiac imaging at screening were added when applicable.
- Section 8.4.2: Modified frequency of ECG monitoring as well as need for triplicate ECG at all timepoints for subjects receiving NIS793, and outlined in new table 8-15 added
- Section 8.4.3: Added new section regarding cardiac enzyme monitoring for all arms containing NIS793.
- Section 8.4.4: Updated cardiac imaging section to include assessments for patients receiving NIS793.
- Section 8.5.2: Deleted "Note c" in Table 8-16 as it is no longer needed.
- [redacted]
- Section 9.1.2: Updated Withdrawal of consent language per Novartis template to include the opposition to use of data/biological samples wording.
- Section 10.1.3: Terminology around SAE reporting time updated to say immediately, without undue delay, under no circumstances later than within 24 hours.
- [redacted]

- Section 15: Additional reference has been added.
- Section 16.6.1: Updated to patients must have been on ruxolitinib for “at least 12 weeks” and must have been on a stable dose for “at least 4 weeks”.
- In addition, clarifications and corrections were made throughout the protocol to improve consistency and understanding.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 5 (23-Feb-2021)

Amendment rationale

At the time of the amendment, 20 subjects have received study treatment in this study in Part 1.

The purpose of this global amendment is to:

- Update the study design to allow 1) Part 2 (Selection) to be conducted for each combination treatment once the combination treatment is determined to be safe and tolerable in Part 1, and 2) to allow more than one combination treatment selected in Part 2 to enter Part 3 (Expansion).
- Add an interim analysis per combination treatment after at least 10 subjects completed 24 weeks of study treatment in Part 2 to allow for a seamless transition into Part 3 if an efficacy threshold is reached.
- Reduce the number of PK and PD samples collected, including removal of a few assessment visits in Part 2 and Part 3 of the study.
- Include specific requirements for conducting the study in China, Japan and USA.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Protocol Summary has been updated with key changes.
- Section 3: Study design has been updated to allow Part 2 to be conducted in one or more groups that will consists of one or more combination treatments and a common ruxolitinib monotherapy arm and that combination treatments may enter Part 2 in a staggered manner. Part 3 has been updated to allow for more than one combination treatment to be expanded. The expected number of subjects in the study has been increased to approximately 240 if all 5 combination treatments enter Part 2 and then only one combination treatment enters Part 3. If all 5 combination treatments are expanded in Part 3, then there will be a maximum of approximately 380 subjects in all 3 parts of the study. Figures 3-1, 3-3 and 3-4 have been updated, accordingly. Two interim analyses are now planned for each treatment combination arm in Part 2.
- Section 4.1: Added two interim analyses per combination treatment in Part 2; and clarified that subjects are not allowed to participate again within the same part of the study, however subjects can participate in other parts of the study provided that all inclusion criteria and none of the exclusion criteria are met.
- Section 4.3.4: Additional rationale for the LTT462 and ruxolitinib combination and corresponding references have been added.
- Section 4.4: A second interim analysis for each combination treatment has been added in Part 2.
- Section 4.5: The sentence on TLS was updated with the current information that one grade 4 TLS was observed in subjects administered siremadlin in study CHDM201X2101. Japan-specific requirements for hospitalization has been added for ruxolitinib + crizanlizumab treatment in Part 1 Arm 2 of the study.

- Section 4.6: Rationale for public health emergency mitigation procedures has been added.
- Section 5: Added wording to state that assuming all five combination treatments enter Part 2 and one combination treatment is expanded in Part 3, a total of approximately 240 subjects are expected to be enrolled in all three parts of the study, and up to approximately 380 if all 5 combination treatments enter Part 3.
- Section 5.1: Inclusion criteria #1 has been updated to add Japan-specific requirements for written consent for subject under the age of 20 years.
- Section 5.2: Exclusion criteria #23 has been updated to reduce the duration between the use of erythropoietin stimulating agents (ESA) and the first dose of study treatment from 3 months to 4 weeks.
- Section 6.1: Added statement in the text and in Table 6-1 that ruxolitinib in USA will be supplied locally as commercially available either by Novartis of the site pharmacy.
- Section 6.1.3: Description of the groups for Part 2 of the study has been added and the number of patients in each treatment arm has been updated accordingly, and to remove reference to any randomization ratio. The same was done for part 3 of the study.
- Section 6.2.2.4: Ruxolitinib + LTT462 was removed from one of the titles as it was not applicable.
- Section 6.3.1: Clarified that subjects will receive a new subject ID if they participate in another part of the study.
- Section 6.3.2: Treatment assignment has been updated to state that Part 2 will be conducted in groups based on the update to the study design; to remove reference to any randomization ratio; that medication numbers will not be provided for the local supply of ruxolitinib in USA; to add randomization numbers in place of a randomization list; and that details of the randomization requirements will be documented in randomization requirement specification document.
- Section 6.5.2: Added a statement that for Japan only, further subjects can be added after the RP2D has been determined to further characterize safety.
- [redacted]
- Section 6.6: Updated the additional treatment guidance for Tumor Lysis Syndrome with the latest available information.
- Section 6.7: Added wording that medication numbers will not be provided for the local supply of ruxolitinib in USA. Also added a statement that during a public health emergency declared by local or regional authorities, delivery of the study treatment directly to a subject's home may be permitted. In such cases regular phone calls or virtual contacts with the subject will also be required.
- Section 6.7.2: Added wording that the assignment of study medication kits by IRT is not applicable for the local supply of ruxolitinib in USA.
- Section 6.7.2.2: Clarification added for the administration of siremadlin in a fasted state.
- Section 7: Statement added that during a public health emergency declared by local or regional authorities, informed consent may be collected remotely as per local guidance.
- Section 8: Japan-specific requirements for hospitalization has been added for ruxolitinib + crizanlizumab treatment in Part 1 Arm 2 of the study. Statement also added that during a

public health emergency declared by local or regional authorities, if allowed by local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

- Section 8: Table 8-1 has been updated to clarify that during the C1D1 visit, the IRT dispensation transaction, the MUGA and the ophthalmologic exam can be performed up to 3 days prior to the first dose. Table 8-2, Table 8-3, Table 8-4 and Table 8-5 have been updated to align with the updated protocol sections. [redacted]
- Section 8.3.2.2 and Section 8.3.2.4: Appearance of a new splenomegaly that is palpable at least 5cm below the LCM has been added as one of the criteria for progressive spleen size requiring a new MRI/CT scan to confirm spleen size progression.
- Section 8.3.2.5: Footnote added to Table 8-7 that bone marrow aspirates collected within 8 weeks of C1D1 for re-screened subjects are acceptable.
- Section 8.4: Statement added that during a public health emergency declared by local or regional authorities that limits or prevents on-site study visits, regular phone or virtual calls can occur for safety monitoring and discussion of the participant´s health status until it is safe for the subject to visit the site again.
- Section 8.4.1: Free T3 has been removed from Table 8-11 as a thyroid function parameter to be analyzed.
- Section 8.4.5: Added statement that if subjects cannot visit the site to have serum pregnancy tests, urine pregnancy test kits may be used. A communication process should be established with the subject so that the site is informed and can verify the pregnancy test results as per country specific requirements.
- [redacted]
- Section 8.5.1: Added statement that during a public health emergency as declared by local or regional authorities that limits or prevents on-site study visits, PROs may be collected remotely depending on local regulations, technical capabilities, and following any applicable training in the required process.
- Section 8.5.2: Added statement that during a public health emergency as declared by local or regional authorities that limits or prevents on-site study visits, changes in PK assessments can be listed as one of the risk mitigation procedures.
- Section 8.5.2: Updated the collection of IG samples, where applicable, to be limited to only the first 10 subjects in Arm 1 (the combination treatment arm) in Part 3.
- Section 8.5.2: Table 8-15, Table 8-18, Table 8-20 and Table 8-21 have been updated to decrease the number of PK and IG samples collected during Part 2 and Part 3 of the study.

- Section 8.5.2: Some of the dose reference IDs in Table 8-15, Table 8-21 and Table 8-22 have been updated.
- Section 8.5.2: Table 8-15, Table 8-18, Table 8-19, Table 8-21 and Table 8-22 have been updated to add a new "Part" column to clarify which Part of the study the PK and IG samples are collected.
- Section 8.5.2: The footnotes in Table 8-16 and Table 8-17 have been updated to limit the collection of IG samples to the first 10 enrolled subjects in Part 3, similar to the PK collection.
- Section 8.5.2: Table 8-22 has been updated to collect PK and IG samples for the Day 30 and Day 90 Safety Follow-up visits for subjects on treatment arms containing NIS793.
- Section 8.5.2.1: Clarified that additional PD samples will not be collected at the 90-day safety follow up visit from subjects treated with sabatolimab, or at the 105-day safety follow up visit from subjects treated with crizanlizumab; and added statement that additional PK, PD and IG samples will be collected at the 30-day and 90-day safety follow up visits for subjects treated with NIS793.
- Section 8.5.2.2: Corrected the LLOQ for the sabatolimab analytical assay to 5.0 µg/mL.
- Section 8.5.3: Added statement that during a public health emergency as declared by local or regional authorities that limits or prevents on-site study visits, [redacted] can be listed as one of the risk mitigation procedures.
- [redacted]
- [redacted]
- Section 9.2: Clarification added that for NIS793 treatment arm, PK, PD and IG samples will be collected at the 30-day and 90-day Safety Follow-up visits.
- Section 10.1.2: Add the word new in reference to "all new malignant neoplasms" in the 3rd last paragraph.
- Section 10.1.4: Updated as per latest protocol guidance.
- Section 12: Added a statement that subjects from the common ruxolitinib monotherapy control arm will be pooled and analyzed jointly; updated the description of the interim analyses to include two interim analyses per combination treatment and that an additional interim analysis for Part 2 will be conducted when at least 10 subjects in the combination treatment arms completed 8 cycles (arms with NIS793) or 6 cycles (all other arms) of treatment; and added a statement that the second interim analysis is not required if a combination treatment is advanced in Part 3 based on the first interim analysis.
- Section 12.1.3: Added a statement that subjects enrolled in Japan after the dose determination for a combination treatment will not be included in the DDS.
- Section 12.4.2.2: Added and explained the efficacy threshold for the first interim analysis.

- Section 12.5.1.2: Added secondary analysis for the proportion of subjects achieving at least 25% and 35% reduction in spleen volume from baseline.
- Section 12.7: Described the two interim analyses for Part 2 and the primary analysis for Part 3.
- Section 12.8.1.2: Added the sample size calculation with operating characteristics for supporting the 1st interim analysis in Part 2.
- Section 12.8.1.3: Updated the probability for possible trial outcome tables in Part 3 for supporting the trial sample size calculation.
- Section 15: Additional references have been added.
- Section 16.7: Added an appendix with simulation for hypothetical study scenarios in Part 2 and Part 3.
- Section 16.8: Added an appendix with a hypothetical example to illustrate enrollment, interim analyses and expansion decision rules for the randomization parts (Parts 2 and 3) of the study design.
- In addition, clarifications and corrections were made throughout the protocol to improve consistency and understanding.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 4 (25-Aug-2020)

Amendment rationale

At the time of the amendment, 13 subjects have received study treatment in this study in Part 1.

The purpose of this global amendment is to:

- Add two novel compounds to Part 1 of the protocol: LTT462, which is a potent, selective, inhibitor of extracellular signal-regulated kinase 1 (ERK1) and extracellular signal-regulated kinase 2 (ERK2), and NIS793, which is an anti-transforming growth factor beta (anti-TGFβ) monoclonal antibody (mAb).
- Add the additional cycles throughout the protocol, where applicable, for NIS793 since the dosing regimen of NIS793 is once every 3 weeks (Q3W) in comparison to all other treatment combinations, which are 28-day cycles. A separate visit assessment schedule for study treatment arms with NIS793 has been added for clarity.
- Increase the number of subjects required for Part 2 from 15 subjects per arm to 25 subjects per arm to ensure the acceptable futility probability for applying the futility rule in multiple arms. The overall number of subjects in the study increases from approximately 130 to approximately 240 in total due to the additional arms for the 2 new compounds in Parts 1 and 2 and the increased number of subjects required per arm for Part 2.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Protocol Summary has been updated with key changes.
- Section 1: Added background information on LTT462 and NIS793.
- Section 2: Updated the primary endpoint for Parts 2 and 3 to clarify that the response rate (RR) is evaluated at the end of 6 cycles or 8 cycles in order to cater for the different cycles lengths with the addition of ruxolitinib + NIS793. The secondary objectives have also been updated for the addition of LTT462 and NIS793.
- Section 3: Added the new combination arms with LTT462 and NIS793, Figure 3-1, Figure 3-2, Figure 3-3 and Figure 3-5 have been updated accordingly. Total number of subjects expected to be enrolled in the study updated to take into account the new treatment arms and the number of subjects in Part 2.
- Section 4.1: Study rationale updated with LTT462 and NIS793.
- Section 4.2.1: Added ruxolitinib is also metabolized by CYP2C9.
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- Section 4.5: Added risks and benefits associated with the addition of LTT462 and NIS793, including an update to the guidance for immune-related events in subjects treated with immunomodulatory therapies such as NIS793 and sabatolimab, and careful monitoring for the possibility of cardiac events and ophthalmological toxicities with LTT462.
- Section 4.5: Added information and guidance for infusion-related reactions (IRRs), particularly for the potential of IRRs such as pain events associated with administration of crizanlizumab in sickle-cell disease (SCD) patients.
- Section 4.5: Added a statement that no substantial additional risk for subject safety due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the coronavirus disease 2019 (COVID-19) pandemic has been identified at this time and therefore the benefit risk remains unchanged.
- Section 5: Updated the inclusionary Hb value (now < 11 g/dL (≤ 6.8 mmol/L)) and increased the total number patients to be enrolled (approximately 240).
- Section 5.1: Inclusion criteria #7 has been updated to increase the hemoglobin level for study eligibility to < 11 g/dL (≤ 6.8 mmol/L).
- Section 5.2: Exclusion criteria #3 has been updated to remove the reference to any studies as this exlusion criteria refers to cancer vaccine and immunotherapy treatment within 6 months of starting study treatment.
- Section 5.2: Updated the definition of severely impaired renal function for exclusion criteria #6 to remove reference to serum creatinine.
- Section 5.2: Exclusion criteria #8 has been updated to clarify that immunodeficiency syndromes are exclusionary if in the opinion of the investigator they are clinically significant.
- Section 5.2: Exclusion criteria #12 has been updated with more details related to uncontrolled congestive heart failure.
- Section 5.2: Exclusion criteria #13 has been updated to clarify that subjects with risk factors for Torsades de Pointe including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia or for whom there is an inability to determine the QTcF interval are also excluded from the study.
- Section 5.2: Exclusion criteria #20 has been updated for the safety follow up periods of treatments with LTT462 and NIS793.
- Section 5.2: Exclusion criteria #21 has been updated to include male subjects who are receiving LTT462.
- Section 5.2: Exclusion criteria #31 has been updated to allow the use of anticoagulant and anti-platelet therapy but exclude subjects with any clinically significant bleeding events within 6 months.
- Section 5.2: Exclusion criteria #32 has been added to exclude subjects with pre-existing retinal vein occlusion (RVO) or current risk factors (apart from the underlying MF) for RVO.
- Section 6.1: Added LTT462 and NIS793 as investigational drugs, and as part of the combination treatment.

- Section 6.1.1: Updated Table 6-1 to add the packaging description of the new investigational drugs: LTT462 and NIS793.
- Section 6.1.2: Consideration for pre medication for subjects receiving crizanlizumab has been added.
- Section 6.1.3: Added LTT462 and NIS793 treatment arms.
- Section 6.1.5: Clarified the duration of treatment in cycles rather than weeks, which is dependent on the treatment arm since NIS793 has 21-day cycles, and all other arms have 28-day cycles.
- Section 6.2.1.1: Added any other anti-coagulant, and anti-platelet (including aspirin ≤ 150 mg/day) drugs to the list of permitted medications that have restrictions.
- Section 6.2.1.1.2: Added ruxolitinib + NIS793 to the list of permitted concomitant therapy requiring caution and/or action.
- Section 6.2.1.1.3: Added the list of permitted concomitant therapy requiring caution and/or action specific to combination arm ruxolitinib + LTT462.
- Section 6.2.2: References to LTT462 and NIS793 added, as appropriate. Drugs that interfere with coagulation or inhibit platelets function removed from the list of prohibited medications for all arms of the study except for aspirin > 150 mg/day.
- Section 6.2.2.1: Added strong inducers of CYP3A4/5 are prohibited within 14 days prior to starting and at any time during the study treatment period for all arms of treatment since ruxolitinib, siremadlin and LTT462 are CYP3A4 substrate (moved from Section 6.2.2.2).
- Section 6.2.2.2: Added ruxolitinib + NIS793 to the list of prohibited medications. Removed strong inducers of CYP3A4/5 to Section 6.2.2.1 (as noted above).
- Section 6.2.2.3: Added the prohibited medications specific to combination arm ruxolitinib + LTT462.
- Section 6.3: Updated the subject numbering and treatment assignment for LTT462 and NIS793.
- Section 6.5.1: Added the rationale for the dose chosen for LTT462 and NIS793. Table 6-3 has been added to define the provisional dose levels for LTT462.
- Section 6.5.2: Added LTT462 and NIS793 to the guidelines for dose escalation and determination of RP2D.
- Section 6.5.3: Added LTT462 and NIS793. Table 6-4 updated with DLT criteria specific to LTT462 and NIS793.
- [redacted]
- Section 6.5.5: Added LTT462 and NIS793 to the follow-up for toxicities, including guidance for immune-related AEs (irAEs) for NIS793.
- Section 6.7.2.5: Added the description of the mode of administration of LTT462.
- Section 6.7.2.6: Added the description of the mode of administration of NIS793.
- Section 8: Tables 8-2 and 8-3 have been updated to align with the updated protocol sections. There are now applicable only for arms with 28-day cycles.

- Section 8: Table 8-4 and 8-5 have been added to present the assessment schedules for Ruxolitinib + NIS793 arm for Part 1 and Part 2 and 3, respectively.
- Section 8.2: Added ECOG and ECG to the list of screening assessments required, as well as clarified the PROs and bone marrow aspirate and biopsy samples required at screening.
- Section 8.3.1.2: Clarified that the MRI/CT scans required for the primary efficacy endpoint of change in spleen volume are the screening (baseline) and the cycle 8 (NIS793 arms) or cycle 6 (all other arms) timepoints. Table 8-6 moved to Section 8.3.2.2.
- Section 8.3.2.2: Added the various MRI/CT scan timepoints required for the secondary efficacy endpoint of change in spleen volume, including Table 8-6 (as noted above).
- Section 8.4.2: Table 8-14 added to list the ECG timepoints for ruxolitinib + LTT462 treatment arm
- Section 8.4.3 added to describe cardiac imaging
- Section 8.4.4 added to describe ophthalmologic assessment
- Section 8.5.2: Table 8-21 added to define the PK blood collection timepoints for LTT462 in combination with ruxolitinib.
- Section 8.5.2: Table 8-22 and 8-23 have been added to define the PK and IG blood collection timepoints for NIS793 in combination with ruxolitinib.
- Section 8.5.2.1: Added the PK, [redacted] and IG blood sampling required for LTT462 and NIS793.
- Section 8.5.2.2: Added bioanalytical methods for the analysis of serum concentrations of NIS793 and anti-NIS793 antibodies.
- [redacted]
- Sections 9 and 10: Safety follow-up periods for LTT462 and NIS793 treatment combination arms added.
- Section 12.1.3: Minimum exposure required definition clarified for each treatment arm.
- Section 12.1.4: Added LTT462 to the evaluable profile for the Pharmacokinetic Analysis Set (PAS).
- Section 12.4.3: Added clarification of evaluation of primary endpoint for subjects who withdraw from study treatment before assessments at the end of Cycle 8 (NIS793 arms) or Cycle 6 (all the other arms).
- [redacted]
- Section 12.7: Added LTT462 to the bayesian logistic regression model (BLRM) for dose decisions and escalations.
- Section 12.8: Updated with the new sample size of 25 subjects (instead of 15) in Part 2 including Table 12-5, Table 12-6 and Table 12-7.
- Section 15: Added references for LTT462 and NIS793.
- Appendices 1 and 2 updated for LTT462 and NIS793.

- Updates were made throughout the protocol to clarify the timepoints for the different treatment arms since ruxolitinib + NIS793 is administered in 21-day cycles, whereas the other treatment combinations of ruxolitinib + siremadlin, ruxolitinib + crizanlizumab, ruxolitinib + sabatolimab and ruxolitinib + LTT462 are administered in 28-day cycles.
- MBG453 has been updated to sabatolimab throughout the protocol.
- In addition, clarifications and corrections were made throughout the protocol to improve consistency and understanding.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 3 (28-Apr-2020)

Amendment rationale

At the time of the amendment, 7 subjects have received study treatment in this study in Part 1 and none of them have been treated with sabatolimab.

The purpose of this global amendment is to implement updates following requests from Health Authorities:

- Update Exclusion Criteria #8 to exclude any patients with known history of HIV as an overall positive benefit risk ratio to include HIV patients with the various novel combination treatments cannot be determined at this stage. In addition, antiretroviral therapy (ART) regimen including strong CYP3A4 inhibitors may lead to the potential drug-drug interaction of one or more study medications.
- Extend the restrictions on the use of live vaccines until the end of the follow-up period after the last dose of crizanlizumab and sabatolimab, which is within 5 half-lives of the study treatment.
- Guidance has been added on the criteria for sabatolimab dose management for dermatological adverse drug reactions (ADRs) and non-immune related toxicities to align with the sabatolimab (MBG453) Investigator's Brochure.
- Guidance has been added that subjects should be monitored carefully for any skin toxicity or mucositis, and that study treatment should be discontinued for any suspected case of Stevens-Johnson syndrome (SJS), or Lyell syndrome/toxic epidermal necrolysis (TEN) to align with the sabatolimab (MBG453) Investigator's Brochure.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Section 5.2: Exclusion Criteria #8 was updated to exclude any subjects with known history of HIV.
- Section 6.2.2.2: The restriction of the use of live vaccines has been extended to 105 days after the last dose of crizanlizumab and to 150 days after the last dose of sabatolimab.
- [redacted]
- Section 6.5.5: Guidance has been added for subjects on sabatolimab that subjects should be monitored carefully for any skin toxicity or mucositis, and that study treatment should be discontinued for any suspected SJS/TEN.
- In addition, corrections have been made throughout the protocol for any typographical errors.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 2 (17-Feb-2020)

Amendment rationale

At the time of the amendment, 3 subjects have received study treatment in this study in Part 1.

The purpose of the amendment is to:

- Clarify the definition of accelerated phase for progression free survival (PFS) as there was a discrepancy between Section 2 (Table 2-1) and Section 8.3.2.4.
- Clarify that subjects who previously participated in the CINC424H12201 study can participate in a subsequent part of the study.
- Remove the exclusion of subjects who have been treated with hematopoietic colony-stimulating growth factors (CSFs) to align with Section 6.2.1.1, where it states that granulocyte growth factors are permitted concomitant therapy requiring caution and/or action.
- Exclude any subjects that have used live vaccines within 30 days of starting any study treatment, and to add live vaccines as prohibited medication for study treatment arms containing crizanlizumab or sabatolimab. This is added considering the safety profile of crizanlizumab and sabatolimab, both of which have immunoregulatory functions.
- Exclude any subjects that have used systemic steroid therapy and other immunosuppressive drugs (> 10 mg/day prednisone or equivalent) within 14 days prior to first dose of study treatment (Topical, inhaled, nasal, and ophthalmic steroids are allowed. Replacement therapy, steroids given in the context of a transfusion are allowed and not considered a form of systemic treatment). The use of systemic steroid therapy was also added as prohibited medication except for treatment of infusion reaction, treatment of immune-related AEs (irAEs), prophylaxis against imaging contrast dye allergy, replacement-dose steroids in the setting of adrenal insufficiency (providing this is ≤ 10 mg/day prednisone or equivalent) or treatment of transient exacerbation of other underlying diseases such as chronic obstructive pulmonary disease requiring treatment for ≤ 3 weeks. This is added considering the safety profile of sabatolimab as a checkpoint inhibitor.
- Exclude any subjects that have used anticoagulation or antiplatelet therapy within 10 days of prior to first dose of study treatment, as well as any subjects that have had any bleeding events within 6 months prior to first dose of study treatment. This aligns with the prohibited concomitant medications in Section 6.2.2.
- Update the prohibition of anticoagulation therapy to allow the use of low molecular weight heparin (LMWH) or Direct Oral Anti-coagulants (DOACs) if used at sub-therapeutic doses, to prevent deep vein thrombosis (DVT) or atrial fibrillation (AF).
- Add erythropoietin stimulating agents (ESAs) as prohibited medication to align with exclusion criteria #23, since ESAs could improve anemia and interfere with the study endpoints.
- Add a new fill volume vial of sabatolimab that will be used in the study.
- Update the dose modification table's specific to the novel agents to remove any reference to ruxolitinib, as the dose modification of ruxolitinib will be guided by the Summary of Product Characteristics (SmPC) for ruxolitinib.

- Allow subjects in Part 1 to continue on study treatment after the planned 6 cycles if, in the opinion of the Investigator, the subject is still deriving clinical benefit.
- Define an 'overall safety period' that is from the date of first administration of study treatment to 30 days after the date of the last administration of ruxolitinib or siremadlin, or 105 days after the date of the last administration of crizanlizumab, or 150 days after the date of the last actual administration of sabatolimab, whichever is later. This is for reporting the safety data within the long safety follow-up period.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Protocol Summary has been updated with key changes.
- Section 1.1.2: Added the trade names for ruxolitinib (Jakavi) and crizanlizumab (Adakveo), and that Adakveo was recently approved in the USA to reduce the frequency of vaso-occlusive crises (VOCs), or pain crises, in adult and pediatric patients aged 16 years and older with sickle cell disease (SCD).
- Section 3: The paragraph on Post-Trial Access (PTA) to study treatment has been deleted as it is already outlined in Section 6.1.5; Footnotes have been added to Figure 3-1 and Figure 3-3 clarifying the number of treatment arms and total subjects in Part 2.
- Section 5: Statement that subjects who were enrolled in one part of the study cannot participate in another part of the study has been removed
- Section 5.1: Inclusion criteria #7 has been updated to add the equivalent mmol/L units for hemoglobin < 10 g/dL, which is ≤ 6.2 mmol/L.
- Section 5.2: Exclusion criteria #3 has been updated to clarify that subjects who previously participated in the protocol are not excluded from participating again in a further part of the study.
- Section 5.2: Exclusion criteria #5 has been updated to add the levels of total bilirubin that are exlcusionary.
- Section 5.2: Exclusion criteria #6 has been updated with conditions on the estimated creatinine clearance.
- Section 5.2: Exclusion criteria #8 has been updated to change known 'confirmed diagnosis' to known 'history' and to clarify that subjects with known HIV infection are excluded only if the infection is not controlled by standard therapy, or have known history of opportunistic infection within the past 12 months, or are receiving an antiretroviral therapy (ART) regimen including strong CYP3A4 inhibitors.
- Section 5.2: Exclusion criteria #23 has been updated to delete the exclusion of subjects that have used G-CSFs.
- Section 5.2: Exclusion criteria #29 has been added to exclude any subjects who have used live vaccines within 30 days of starting study treatment.
- Section 5.2: Exclusion criteria #30 has been added to exclude any subjects who use systemic steroid therapy and other immunosuppressive drugs within 14 days prior to first dose of study treatment (> 10 mg/day prednisone or equivalent), noting that topical, inhaled, nasal,

and ophthalmic steroids are allowed, and that replacement therapy, steroids given in the context of a transfusion are allowed and not considered a form of systemic treatment.

- Section 5.2: Exclusion criteria #31 has been added to exclude any subjects who use anticoagulation (prophylactic doses permitted) or antiplatelet therapy (other than aspirin) within 10 days of starting study treatment, or any bleeding events within 6 months prior to first dose of study treatment.
- Section 6.1.1: Updated Table 6-1 to add a new formulation of sabatolimab.
- Section 6.1.5: Post-Trial Access (PTA) wording has been updated in accordance with the latest guidelines.
- Section 6.2.1.1: The condition pertaining to G-CSF not being allowed while study medication is being administered has been deleted.
- Section 6.2.2: Use of systemic steroid therapy and other immunosuppressive drugs within 14 days prior starting treatment and at any time during the study treatment was added to the list of prohibited medications; The prohibition of anticoagulation therapy was updated to allow the use of LMWH or DOACs if used at sub-therapeutic doses; Restrictions on the use of live vaccines after starting treatment were added for certain treatment arms.
- Section 6.5.4: Instructions added for the occurrence of potentially overlapping toxicity or if it cannot be distinguished which of the study drugs within the combination treatment is suspected to be related to an adverse event; Table 6-4, [redacted]
- Section 8: Wording has been added to state that the planned duration of Part 1 is 6 cycles of study treatment.
- Section 8: Table 8-1 has been updated to clarify that only C1D1 does not have a visit window for assessments and administration of study drugs, and that all D1 visits of subsequent cycles have a ± 3-day window; Table 8-2 and Table 8-3 have been updated to align with the updated protocol sections.
- Section 8.2: The screening assessments have been updated to remove the assessment of serology and cytokines (moved to Cycle 1 Day 1) as these two analyses are dependent on the combination treatment arm.
- Section 8.3.1.2: Reference to measuring spleen volume by the least squares method has been deleted.
- Section 8.3.2.4: Corrected the definition of accelerated phase for PFS to align with the definition in Section 2 (Objectives and endpoints).
- Section 8.4.1: Table 8-9 has been updated to clarify that: Bands will no longer be collected as part of the white blood cell differential. Direct Bilirubin will now only be collected if Total Bilirubin is ≥ Grade 2; Indirect Bilirubin will now only be collected if Total Bilirubin is out of range; and the urinalysis microscopic panel will be required only if clinically indicated based on the results of the macroscopic panel analysis. A note was added to clarify that serology is only required for patients in treatment combination arms with sabatolimab and cytokines is only required for patients in treatment combination arms with crizanlizumab or sabatolimab, and that these two assessments will now be performed pre-dose at C1D1 instead of at baseline.

- Section 8.4.3: Clarification added that pregnancy assessment at the beginning of each cycle could be performed via urine or serum testing, however serum testing is the preferred method.
- Section 8.5.1: Updated the calculation of the Total Symptom Score (TSS) to match the user manual for the MFSAF ePRO, and updated the wording in the paragraph describing the Trial Feedback Questionnaire.
- Section 8.5.2: Removed sample 233 in Table 8-12, as it is not applicable at this visit; Note added in Table 8-13 and Table 8-14 to clarify that when there are two Dose Reference ID the first number is for the current dose, while the second is for the last (previous) dose received prior to the collection of the PK sample.
- [redacted]
- Section 9.2: Post-study treatment paragraph deleted as PTA is already described in section 6.1.5.
- Sections 9.2 and 10.1: Added instructions on the collection of new AEs and SAEs for subjects who begin new antineoplastic medication (other than study treatment) before the end of the safety follow-up period.
- Section 12.1.4: Clarification added that a PK profile is evaluable if the subject does not vomit within 2 hours after oral dosing of ruxolitinib in treatment arms that do not contain siremadlin.
- Section 12.5.2: Updated the definition for on-treatment period and post-treatment period following the protocol standard language and defined the 'overall safety period' for reporting the safety data within the long safety follow-up period; Updated the corresponding AE analysis for the defined safety periods; eleted the provision of the ECG summary statistics by visit/time.
- In addition, clarifications and corrections were made throughout the protocol to improve consistency and understanding.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 1 (18-Jul-2019)

Amendment rationale

At the time of the amendment, the study has not started in any of the participating countries/sites.

The purpose of the amendment is to:

- Exclude any subjects from the study that are eligible for allogeneic hematopoeitic stem cell treatment (ASCT). Patients eligible for ASCT should not be prevented from such curative treatment by participating in the clinical trial.
- Clarify that any subjects that are scheduled for ASCT during the study must be discontinued to ensure that eligible patients for ASCT are not prevented from curative ASCT treatment.
- Align updated information available from the sabatolimab (MBG453) Investigator's Brochure to use highly effective forms of contraception for women of child-bearing potential (WOCBP) for up to 150 days for subjects on study treatment that includes sabatolimab.
- Clarify that the safety follow-up for subjects on study treatment that includes sabatolimab is up to 150 days in accordance with the sabatolimab (MBG453) Investigator's Brochure. Safety Follow-up visits are now conducted at 30 days, 90 days and 150 days.
- Exclude all forms of hormonal contraception for WOCBP since the effectiveness of hormonal contraception can potentially be reduced with the possible induction of CYP3A4 by siremadlin. For consistency, hormonal contraception has been excluded from all arms of the study.
- Exclude any subjects that cannot discontinue drugs that strongly induce or inhibit CYP2C9 since ruxolitinib is metabolised by CYP2C9
- Add strong inducers or inhibitors of CYP2C9 as prohibited medications, and to advise caution on the use of moderate inducers or inhibitors of CYP2C9 since ruxolitinib is metabolised by CYP2C9.
- Clarify the safety run-in of crizanlizumab and sabatolimab arms of the study in Part 1, that if 2 subjects experience a DLT in either arm, then further enrolment into that arm will stop, and the treatment combination will not open in Part 2.
- Clarify that intra-subject dose escalation is not allowed in this study. This was left out of the original protocol.
- Add additional ECG safety monitoring for any QTc interval prolongation > 60 msecs from baseline per the ICH E14 guidelines.
- Add a recommendation for all subjects to protect their skin from solar UV radiation if they are on study treatment that contains siremadlin as there is a potential for phototoxicity with siremadlin (in vitro findings).
- Clarify that soft centimeter rulers will not be provided to investigators to measure the palpable spleen length as this can be acquired by the site.
- [redacted]

[redacted]

- Clarify that urine pregnancy tests will be performed monthly for all pre-menopausal women who are not surgically sterile to ensure appropriate pregnancy monitoring for all WOCBP.
- Add further hypothetical on-study data scenarios to the Bayesian model used to guide dose escalation in Part 1 for siremadlin in combination with ruxolitinib to further demonstrate the performance of the Bayesian Logistic Regression Model (BLRM).

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Section 3: Figure 3-2, Figure 3-3, and Figure 3-5 have been updated for the extended safety follow-up of up to 150 days for sabatolimab.
- Section 5.2: Exclusion criteria #20 has been updated to clarify that WOCBP should use highly effective methods of contraception for up to 150 days after the last dose of sabatolimab.
- Section 5.2: Exclusion criteria #20 has been updated to exclude all forms of hormonal contraception for WOCBP.
- Section 5.2: Exclusion criteria #27 has been updated to exclude any subjects that cannot discontinue drugs that strongly induce or inhibit CYP2C9.
- Section 5.2: Exclusion criteria #28 has been added to exclude any patient that is eligible for ASCT from entering the study.
- Section 6.2.1.1: Added statement to advise that the use of moderate inducers or inhibitors of CYP2C9 requires caution.
- Section 6.2.2: Added statement that strong inhibitors or inducers of CYP2C9 are prohibited medications.
- Section 6.5.2: Updated sentence to clarify that if 2 subjects in either arm with crizanlizumab (Arm 2) or sabatolimab (Arm 3) experience a DLT, further enrollment into that arm will stop and that combination treatment will not open in Part 2.
- Section 6.5.2.2: Added a sentence to state that intra-subject dose escalation is not allowed in the study.
- Section 6.5.4: Added a sentence as a footnote to rash/photosensitivity that it is recommended that subjects should protect their skin from solar UV radiation while on any study treatment that includes siremadlin.
- Section 6.5.4.1: Increased ECG safety monitoring has been added for QTc prolongation > 60 msec from baseline.
- Section 6.5.5, Section 9.2, Section 10.1.1, Section 10.1.3 and Section 12.5.2: Updates have been made throughout the protocol for the extended safety follow-up of up to 150 days for sabatolimab.
- Section 8.3.2.2: Removed the sentence that states investigators will be provided with a soft centimeter ruler to measure the length of the palpable spleen.

- Section 8.4.3: Clarified that additional urine pregnancy testing will be performed at the beginning of every cycle for all pre-menopausal women who are not surgically sterile.
- [redacted]
- Tables 8-1, 8-2 and 8-3: Updates made to the tables to be in alignment with the updated protocol sections.
- Section 9.1.1: Added a sentence to clarify that any subject that is scheduled for ASCT during the course of the study must be discontinued from the study treatment.
- Section 16.1 (Appendix 1): Updated Table 16-1 to add moderate inhibitors and inducers of CYP2C9.
- Section 16.2 (Appendix 2): Updated Table 16-2 to add strong inhibitors and inducers of CYP2C9.
- Section 16.6.4 and Table 16-7: Additional wording and scenarios have been added to the hypothetical dose escalations scenarios for siremadlin
- In addition, clarifications and corrections were made throughout the protocol to improve consistency and understanding.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Protocol summary

Protocol number	CINC424H12201
Full Title	A randomized, open-label, phase I/II open platform study evaluating safety and efficacy of novel ruxolitinib combinations in myelofibrosis patients
Brief title	A safety, pharmacokinetics and preliminary efficacy study of novel ruxolitinib combination treatments in patients with myelofibrosis
Sponsor and Clinical phase	Novartis, phase Ib/II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Myelofibrosis (MF) is defined by progressive bone marrow (BM) fibrosis and a consecutive reduction of blood cells. The disruption of the medullary erythropoietic niche is the primary mechanism governing the bone marrow failure and anemia, which typify MF. Nearly 40% of MF patients have hemoglobin (Hb) levels < 10 g/dL at diagnosis. Furthermore, anemia is the disease feature most consistently associated with poor prognosis in MF. Ruxolitinib demonstrates improvements in splenomegaly and constitutional symptoms, however, does not improve anemia. The purpose of this study is to investigate the safety, pharmacokinetics (PK) and preliminary efficacy of combinations treatment of ruxolitinib with 5 novel compounds: siremadlin, crizanlizumab, sabatolimab, rineterkib and NIS793 in MF subjects. These combination therapies may deliver transformational clinical benefits such as improvement of progression free survival (PFS) as a consequence of superior disease control or reduction of the malignant clone, associated with an improvement of cytopenia and in particular anemia, as well as improvement in quality of life (QoL) as captured by relevant patient reported outcomes measurements (PROs). Novartis decided to permanently halt the enrollment of CINC424H12201. An extension treatment phase was introduced in Part 1 with amended protocol version 08 to allow access to the investigational drug combination to ongoing subjects deriving clinical benefit. The duration of the extension treatment phase was increased to a maximum of 21 cycles with amended protocol version 09.
Primary Objective(s)	The primary objective of Part 1 of this study is to characterize the safety, tolerability, and the recommended Phase 2 dose (RP2D) of each combination partner used with ruxolitinib in subjects with myelofibrosis. This is assessed by the incidence and severity of dose-limiting toxicity (DLTs) within the first 2 treatment cycles in Part 1 of the study. The primary objective of Parts 2 and 3 of the study is to evaluate the preliminary efficacy of the novel ruxolitinib combination treatments in subjects with myelofibrosis. This is based on the assessment of the response rate (RR) at the end of Cycle 8 for all arms containing NIS793 or Cycle 6 for all other arms. The RR is the composite of anemia improvement of ≥ 1.5 g/dL, no spleen volume progression and no symptom worsening. As the enrollment was permanently halted, not all planned study objectives for Parts 1, 2, and 3 could be completed. All Parts 2 and 3 objectives will not be pursued. [redacted]
Secondary Objectives	• To assess the proportion of subjects in each treatment arm who achieve an Hb improvement of ≥ 2.0 g/dL or ≥ 1.5 g/dL from baseline (Parts 2 & 3) • To evaluate changes in symptoms of myelofibrosis in each treatment arm using Myelofibrosis Symptom Assessment Form (MFSAF) v4.0 and European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) patient reported outcomes (PROs) from baseline (Parts 2 & 3) • To characterize the pharmacokinetic profile of ruxolitinib administered in combination with siremadlin, crizanlizumab, sabatolimab, rineterkib and NIS793 respectively (Parts 1, 2 & 3) • To assess emergence of anti-crizanlizumab, anti-sabatolimab or anti-NIS793 antibodies following one or more IV infusions (Parts 1, 2 & 3) • To evaluate the changes in spleen size in each treatment arm measured by change in spleen length (by palpation) and spleen volume (by magnetic resonance imaging (MRI)/computed tomography (CT)) from baseline (Parts 2 & 3)

	• To evaluate the effect of each ruxolitinib combination treatment in delaying progression of MF and estimate time to progression free survival (PFS) event (Parts 2 & 3) • To evaluate the effect on bone marrow fibrosis in each treatment arm by determining the proportion of subjects achieving improvement in bone marrow fibrosis of ≥ 1 grade from baseline (Parts 2 & 3) • To evaluate long-term safety and tolerability of ruxolitinib combination treatments in each arm based on frequency, duration and severity of adverse events (AE), abnormalities in vital signs and laboratory test values, including electrocardiogram (ECG) data (Parts 1, 2 & 3) In consideration of the enrollment halt, a number of preplanned study objectives will not be pursued. All Parts 2 and 3 objectives will not be pursued. [redacted] The following objectives were added or edited as secondary objectives: • To evaluate the changes in spleen size in each treatment arm (Part 1 core and extension, Part 2 & 3) • To evaluate changes in symptoms of myelofibrosis in each treatment arm using MFSAF v4.0 (Part 1) • To evaluate safety and tolerability of ruxolitinib combination treatments in each arm (Part 1 core and extension, Part 2 & 3)
Study design	This is an open-label, multi-center, phase Ib/II platform study consisting of 3 parts that will enroll approximately 240 subjects in total, assuming that 5 novel combination treatments from Part 1 are selected for Part 2, and that 1 of the 5 novel combination treatments is expanded in Part 3. If all 5 combination treatments enter Part 3, then there will be a maximum of approximately 380 subjects in total in all 3 parts of the study. Part 1 is a phase Ib dose escalation and safety run-in for the 5 novel agents in combination with ruxolitinib to assess safety, tolerability and to confirm recommended Phase II dose. Approximately 18 subjects in total will be enrolled in 3 dose escalation cohorts for ruxolitinib + siremadlin treatment, and approximately 12 subjects in total will be enrolled in 2 dose escalation cohorts for ruxolitinib + rineterkib treatment. In the safety run-in, approximately 6 subjects will be enrolled for each arm of ruxolitinib + crizanlizumab, ruxolitinib + sabatolimab, and ruxolitinib + NIS793. Eligible subjects in Part 1 will be treated for a planned duration of 8 cycles (arms with NIS793) or 6 cycles (all other arms), where a cycle consists of 21 or 28 days, depending on the treatment arm (24 weeks), however a minimal of 2 cycles of treatment will be used to evaluate whether the combination treatment is eligible for Part 2. In the context of the permanent enrollment halt, the 3 parts study design has been revised with Part 1: Dose escalation and safety-run-in to include a core treatment phase and an extension treatment phase, Part 2: Selection remained unchanged as the only randomized subject has discontinued prior to amended protocol version 08 and Part 3: Expansion will not be applicable as it will never be initiated. Parts 2 and 3 are a phase II selection and expansion, respectively, to assess preliminary efficacy of the combination treatments from Part 1 that are evaluated as safe and tolerable. Part 2 will be conducted in groups and will consist of a maximum of 6 arms of treatment, one arm for each of the 5 novel combinations plus a common ruxolitinib monotherapy control arm. The number of arms will depend on the results of the Part 1 dose escalation and safety run-in phase in Part 1. A maximum of 155 subjects will be randomized to combination treatments and ruxolitinib monotherapy for a planned duration of 12 cycles or 16 cycles of treatment (48 weeks), depending on the treatment arm. Each combination treatment arm will enroll approximately 25 subjects, and the common ruxolitinib monotherapy control arm will enroll approximately 30 subjects assuming 3 groups in Part 2. Two interim analyses are planned in Part 2 for each combination treatment arm. The two interim analyses will be performed after respectively at least 10 and 25 subjects in the combination treatment arms have completed 6 cycles or 8 cycles of treatment, depending on the treatment arm (24 weeks), to determine whether the combination treatment is expanded in Part 3. For each selected combination treatment, Part 3 of study is expected to consist of the combination treatment(s) chosen from Part 2, the ruxolitinib cessation arm(s) (novel agent monotherapy), and a common ruxolitinib monotherapy control arm. Subjects will be randomized with a planned enrollment of

	approximately 20 subjects for a combination treatment arm, 10 subjects for a ruxolitinib cessation arm (novel agent monotherapy) for Part 3, and maximum 50 subjects for the ruxolitinib monotherapy arm for Part 2 and Part 3 in total. Part 1 is updated to include a core treatment phase and an extension treatment phase. The end of core treatment phase will occur when amended Protocol version 08 is implemented, after a minimum of 24 weeks of treatment in the core phase. The planned duration for the extension treatment phase is maximum 21 cycles (84 weeks) when amended protocol version 09 is implemented. Core treatment phase and extension treatment phase are not applicable to Parts 2 and 3.
Population	The patient population will include male or female adults (age 18 or over) with a confirmed diagnosis of PMF or PPV- MF, or PET- MF.
Key Inclusion criteria	Key inclusion criteria are listed below, please refer to the protocol for the full list of inclusion criteria: • Subjects have diagnosis of primary myelofibrosis (PMF) according to the 2016 World Health Organization (WHO) criteria, or diagnosis of post-essential thrombocythemia (ET) (PET-MF) or post-polycythemia vera (PV) myelofibrosis (PPV-MF) according to the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) 2007 criteria. • Palpable spleen of at least 5 cm from the left costal margin (LCM) to the point of greatest splenic protrusion or enlarged spleen volume of at least 450 cm3 per MRI or CT scan at baseline (a MRI/CT scan up to 8 weeks prior to first dose of study treatment can be accepted). • Have been treated with ruxolitinib for at least 12 weeks prior to first dose of study treatment. • Are stable (no dose adjustments) on the prescribed ruxolitinib dose (between 5 and 25 mg twice a day (BID)) for ≥ 4 weeks prior to first dose of study treatment. • Hemoglobin < 11 g/dL (≤ 6.8 mmol/L). • Part 1: Platelet counts ≥ 75,000/μL. • Part 2 and Part 3: Platelet counts ≥ 50,000/μL. Key inclusion criteria for the extension treatment phase are listed below, please refer to the protocol for the full list of inclusion criteria: • Signed informed consent form prior to participation • Ongoing in the core treatment phase • Demonstrated clinical benefit in the core treatment phase per investigator's assessment.

Key Exclusion criteria	Key exclusion criteria are listed below, please refer to the protocol for the full list of exclusion criteria:
	• Not able to understand and to comply with study instructions and requirements.
	• Received any investigational agent for the treatment of MF (except ruxolitinib) within 30 days of first dose of study treatment or within 5 half-lives of the study treatment, whichever is greater.
	• Peripheral blood blasts count of > 10%.
	• Had documented severe hypersensitivity reactions/immunogenicity (IG) to a prior biologic product in any treatment arm OR received a monoclonal antibody or immunoglobulin-based agent:
	  • For treatment arms with NIS793, crizanlizumab or sabatolimab within 1 year of screening,
	  • For treatment arms with rineterkib or siremadlin arms within <=4 weeks of screening or <=5 half lives whichever is shorter for rineterkib or siremadlin arms
	  • For Part 2 and Part 3, the longest window will apply based on the compounds opened for randomization.
	• Splenic irradiation within 6 months prior to the first dose of study drug.
	• Received blood platelet transfusion within 28 days prior to first dose of study treatment. (Note: PRBC transfusions are permitted)

	• Subjects with known TP53 mutation or deletion of TP53. • Use of systemic steroid therapy and other immunosuppressive drugs within 14 days prior to first dose of study treatment (> 10 mg/day prednisone or equivalent). Topical, inhaled, nasal, and ophthalmic steroids are allowed. Replacement therapy, steroids given in the context of a transfusion are allowed and not considered a form of systemic treatment. • Occurrence of any clinically significant bleeding events within 6 months prior to first dose of study treatment. • For patients treated with rineterkib in Part 1 and for all patients in Part 2 and Part 3 (if an rineterkib arm is included in the randomization for Part 2 or Part 3): Pre-existing retinal vein occlusion (RVO) or current risk factors (apart from the underlying MF) for RVO. Key exclusion criteria for the extension treatment phase are listed below, please refer to the protocol for the full list of exclusion criteria: • Subject meeting the list of discontinuation criteria • Evidence of treatment failure • Enrollment in another interventional study • Subject has evidence of non-compliance to study procedures or withdrew consent in core treatment phase • Unresolved toxicities for which treatment has been interrupted in the core treatment phase • Subject has local access to alternative myelofibrosis treatment as assessed suitable in the opinion of the investigator.
Study treatment	Ruxolitinib (INC424), siremadlin (HDM201), crizanlizumab (SEG101), sabatolimab (MBG453), rineterkib (LTT462), NIS793
Efficacy assessments	The efficacy assessments for the primary objectives are: • Laboratory hemoglobin assessments taken at the end of Cycle 8 for all arms containing NIS793 or Cycle 6 for all other arms compared to baseline • MRI or CT imaging of the spleen performed at the end of Cycle 8 (for NIS793) or Cycle 6 (for all other arms) compared to baseline • Total symptom score (TSS) assessed by MFSAF v4.0 at baseline and at the end of. Cycle 8 (for NIS793) or Cycle 6 (for all other arms) The efficacy assessments for the secondary objectives are: • Laboratory hemoglobin assessments • Manual palpation and MRI/CT imaging of the spleen • MFSAF v4.0 and EORTC QLQ-C30 patient reported outcomes (PROs) • Disease progression events assessed by progressive splenomegaly, accelerated phase, deteriorating cytopenia, leukemic transformation or death • Bone marrow fibrosis and histomorphology assessment of bone marrow biopsy and aspirate • Clinical benefit assessment per investigator's opinion for extension treatment phase
Pharmacokinetic assessments	• PK parameters (e.g., AUC, Cmax, Tmax) and concentration vs. time profiles of each investigational drug within combination regimens • IG samples to monitor appearance of antidrug antibodies (ADAs) directed against crizanlizumab, sabatolimab or NIS793 • PK assessments are not applicable for the extension treatment phase • The investigators were instructed prior to the implementation of the amended protocol version 08 to not collect pharmacokinetic, immunogenicity [redacted] samples from subjects in Part 1 all treatment arms to reduce subject burden.
Key safety assessments	• Physical examination • Eastern Cooperative Oncology Group (ECOG) performance status • Weight and vital signs • 12-lead ECG

	• Laboratory assessments including hematology, chemistry, urinalysis, coagulation, thyroid function, serology, safety cytokines • Pregnancy testing for women of childbearing potential • Adverse events (AEs): severity, relationship to study treatment and seriousness • For LTT462 arms: cardiac imaging and ophthalmological assessments • For NIS793 arms: cardiac imaging and cardiac assessments (troponin I, NTproBNP)
Other assessments	[redacted]
Data analysis	Part 1 primary analysis Identification of the RP2D of siremadlin in combination with ruxolitinib or rineterkib in combination with ruxolitinib will be based upon the estimation of the probability of DLT within the first 2 cycles for patients in the respective Dose-Determining Set (DDS). The dose escalation will be guided by a Bayesian analysis of dose-limiting toxicity (DLT) data from Cycle 1 and Cycle 2. For the crizanlizumab arm, the sabatolimab arm, and the NIS793 arm the DLT probability is determined as the number of patients in the DDS who experienced a DLT divided by the number of patients in the DDS. Part 2 and Part 3 primary analysis. Analysis on the protocol defined primary endpoint is not applicable for Part 2 and Part 3 due to enrollment halt. Data collected for Part 2 will be reported. The primary clinical study report (CSR) will include analyses on all subject data at the time when the last subject completed the end of treatment visit for core treatment phase (Part 1) and after all subjects have completed at least, 8 cycles (arms with NIS793) or 6 cycles (all other arms) of treatment (24 weeks), or discontinued earlier (Part 1 and Part 2). All extension treatment phase data will be reported in the final CSR after all subjects discontinue from the study or complete the extension treatment phase (maximum 21 cycles) whichever comes last. Due to the permanent enrollment halt, the description for Part 2 and Part 3, including interim analysis are no longer applicable.
Key words	Myelofibrosis, ruxolitinib (INC424), siremadlin (HDM201), crizanlizumab (SEG101), sabatolimab (MBG453), rineterkib (LTT462), NIS793, platform study.

1 Introduction

1.1 Background

1.1.1 Overview of disease pathogenesis, epidemiology and current treatment

Myelofibrosis (MF) is a Philadelphia chromosome-negative myeloproliferative neoplasm (MPN) characterized by the presence of megakaryocyte proliferation and atypia, usually accompanied by either reticulin and/or collagen fibrosis (Tefferi and Vardiman 2008). Additional clinical features include splenomegaly (due to extramedullary hematopoiesis), anemia (due to bone marrow failure and splenic sequestration), and debilitating constitutional symptoms (due to overexpression of inflammatory cytokines) that include fatigue, weight loss, pruritus, night sweats, fever, and bone, muscle, or abdominal pain (Naymagon and Mascarenhas 2017, Abdel Wahab and Levine 2009, Mesa et al 2007). MF is defined by the National Institutes of Health (NIH) as a "rare disease" with a prevalence of 0.3 to 1.5 cases per 100 000 with median age at diagnosis of 65 years (Mehta et al 2014, Rollison et al 2008).

MF can develop de novo, as a primary hematologic malignancy, primary myelofibrosis (PMF) or arise from the progression of preexisting myeloproliferative neoplasms, namely: polycythemia vera (PV) or essential thrombocythemia (ET) (Naymagon and Mascarenhas 2017, Mesa et al 2007). The World Health Organization (WHO) classification system for hematopoietic tumors was recently revised and the 2016 document recognizes several major categories of myeloid malignancies including MPN. Within the WHO MPN category, PMF, PV and ET are operationally grouped together as " JAK2 MPN ". Furthermore, some patients with ET or PV develop a PMF-like phenotype over time, referred to as post-ET (PET-MF) or post-PV MF (PPV-MF), with similar treatment and outcome (Tefferi and Barbui 2019).

Patients with MF have shortened survival (median survival is 6.5 years) and greatly compromised quality of life (QoL). Contributing factors for shortened survival include leukemic transformation and thrombohemorrhagic complications and for the compromised quality of life severe anemia (often requiring red blood cell (RBC) transfusions), symptomatic enlargement of the spleen and liver, substantial MF-associated symptoms burden (MF-SB), and cachexia (Tefferi and Barbui 2019).

The only potential curative treatment for MF is allogeneic hematopoietic stem cell transplantation (ASCT), for which the great majority of patients are ineligible. Therefore, treatment options remain primarily palliative and aimed at controlling disease symptoms, complications and improving the patient's QoL. The therapeutic landscape of MF has changed with the discovery of the V617F mutation of the Janus kinase JAK2 gene present in 60% of patients with PMF or PET-MF and in 95% of patients with PPV-MF, triggering the development of molecular targeted therapy for MF (Cervantes 2014). JAKs play an important role in signal transduction following cytokine and growth factor binding to their receptors. Aberrant activation of JAKs has been associated with increased malignant cell proliferation and survival (Valentino and Pierre 2006). JAKs activate a number of downstream signaling pathways implicated in the proliferation and survival of malignant cells including members of the Signal Transducer and Activator of Transcriptions (STAT) family of transcription factors.

JAK inhibitors were developed to target JAK2 thereby inhibiting JAK signaling. Ruxolitinib, as all agents of this class, mainly inhibits dysregulated JAK-STAT signaling present in all MF patients irrespective of their JAK2 mutational status, but is not selective for the mutated JAK2, which explains its efficacy in both JAK2-positive and -negative MF. Ruxolitinib is highly effective in reducing the spleen size and controlling the symptoms of MF, with this resulting in a marked improvement in the patient's QoL (Cervantes et al 2016). Ruxolitinib is the only JAK inhibitor that has been granted a marketing authorization, as a single agent, for the treatment of patients with PMF, PPV-MF or PET-MF and for the treatment of patients with PV who are resistant to or intolerant to hydroxyurea. Ruxolitinib is the only approved pharmacological treatment for MF patients with splenomegaly and/or clinical symptoms and is considered standard of care (SoC). Although ruxolitinib has changed the treatment paradigm of MF patients, there is no clear indication of its disease-modifying effect (Cervantes 2014) and therapy-related anemia is often an anticipated downside (Naymagon and Mascarenhas 2017, Mead et al 2015). Combination therapies of ruxolitinib with novel agents may deliver transformational clinical benefits such as improvement of anemia and progression free survival (PFS) by better controlling or even reducing the malignant clone.

1.1.2 Introduction to Investigational treatments

The investigational treatment for this trial is the combination of ruxolitinib with one of five novel compounds: siremadlin, crizanlizumab, sabatolimab, rineterkib or NIS793.

1.1.2.1 Ruxolitinib: an inhibitor of JAK1, JAK2 and mutated JAK2V617 signaling

Ruxolitinib (INC424, Jakavi®, Jakafi®) is a potent inhibitor of Janus Kinase (JAK) 1 and JAK2 with modest to marked selectivity against TYK2 (tyrosine kinase 2) and JAK3. Ruxolitinib interferes with the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. Dysregulated JAK-STAT signaling, via upregulation of JAK1 and JAK2 or gain of function mutations such as JAK2V617F, has been implicated as a driver of BCR-ABL (breakpoint cluster region abelson)-negative MPNs, namely MF, PV and ET. Ruxolitinib through binding to and inhibiting of JAK1, JAK2 and mutated JAK2V617F, leads to inhibition of growth factor-mediated cell signaling and tumor cell proliferation.

Ruxolitinib is currently approved under the trade name of 'Jakavi®' in over 100 countries for the treatment of disease-related splenomegaly or symptoms in adult patients with PMF, PPV-MF and PET-MF. The use of ruxolitinib to treat PV patients who are resistant to or intolerant of hydroxyurea is currently approved in more than 60 countries worldwide including Europe.

Ruxolitinib is also approved in the United States of America (USA) under the trade name of 'Jakafi®' and is indicated for the treatment of patients with intermediate- or high- risk myelofibrosis, including PMF, PPV-MF and PET-MF, for the treatment of PV patients who have had an inadequate response to or are intolerant of hydroxyurea .

Ruxolitinib is also approved for the treatment of patients aged 12 and older with acute or chronic graft versus host disease (GvHD) in several countries, including the USA, the European Union, United Kingdom, Australia and Brazil.

Detailed information about the safety and efficacy of ruxolitinib is provided in the Investigator's Brochure.

1.1.2.2 Siremadlin: an inhibitor of HDM2 and modulator of p53 activation

Siremadlin (HDM201) is a novel small molecule inhibitor that targets Human Double Minute-2 (HDM2) by inhibiting its interaction with p53, an intracellular tumor suppressor protein that regulates the cell cycle. The p53 function is frequently compromised in tumor cells (Levine and Oren 2009, Vogelstein et al 2000).

Under physiological conditions, activation of p53 pathway is tightly controlled (Millard et al 2011, Xiao et al 2000), however p53 can be induced and activated by a variety of potentially tumorigenic stress factors, including aberrant growth signals, DNA damage, a range of chemotherapeutic drugs, ultraviolet light, and protein-kinase inhibitors (Millard et al 2011). These pathways maintain a high concentration of intracellular p53, which modulates the expression of genes controlling cell growth arrest, DNA repair, and induces apoptosis of DNA damaged or mutated cells and new blood vessel formation (Vogelstein et al 2010, Bullock and Fersht 2001).

Inactivating mutations in the TP53 gene are found in approximately 50% of all human cancers. In cancers in which the TP53 gene is not mutated, the function of the p53 pathway is often suppressed. This is owing to perturbation of its associated pathways through mechanisms that affect its stability and activity, with overexpression of HDM2 or silencing of p14 ARF (alternate reading frame) being two clinically important mechanisms (Eischen and Lozano 2009, Van Maerken et al 2009, Zhang et al 1998).

Different strategies to restore the p53 function in tumors have been attempted, e.g. the design of antagonists for negative regulators of p53 in tumors carrying wild-type (WT) p53 (Vassilev LT 2007), reactivation of mutant p53 (Joerger and Fersht 2008, Bullock and Fersht 2001), and exogenous p53 expression, e.g., via adenovirus-mediated gene transfer (Roth JA 2006). Two studies on transgenic mice, in which p53 expression was reversibly switched on and off, have independently shown that restoration of the p53 function can lead to tumor regression *in vivo*, indicating that reactivating p53 is a promising therapeutic strategy (Ventura et al 2007, Martins et al 2006).

HDM2 is one of the most important negative regulators of p53. Inhibition of the p53-HDM2 protein-protein interaction using small molecules as a means to antagonize negative regulators of p53 and thus activate p53, has been focused on the p53 binding pocket of HDM2. As such, inhibiting the interaction between HDM2 and p53 represents an attractive and promising therapeutic approach against multiple types of solid and hematological cancers (Saha et al 2013, Capdevila et al 2012, Millard et al 2011).

Siremadlin, by preventing HDM2-p53 interaction, inhibits the proteasome–mediated enzymatic degradation of p53, which may result in the restoration of both p53 signaling and p53-mediated induction of tumor cell apoptosis (Levine and Oren 2009). The goal of treatment with siremadlin is to increase the levels of intracellular p53 through antagonism of HDM2 and thereby activate downstream effector pathways that decrease cell proliferative events. Thus, the efficacy of siremadlin depends on the presence of wild-type p53. As almost all MF patients

have non-mutated p53WT, therefore Siremadlin may offer enhanced clinical benefit in these patients.

Siremadlin is being evaluated as a treatment for several oncology indications including solid and hematological tumors characterized by wild-type TP53 (CHDM201X2101), liposarcoma (CHDM201X2103C), and acute myeloid leukemia (AML). Detailed information about siremadlin safety and efficacy is provided in the Investigator's Brochure.

1.1.2.3 Crizanlizumab: an anti-P-selectin monoclonal antibody

Crizanlizumab (SEG101, Adakveo®) is a recombinant humanized IgG2 kappa anti-P-selectin monoclonal antibody (Ab). The target of crizanlizumab is P-selectin, an adhesion receptor expressed on the surface of activated endothelial cells and platelets. P-selectin plays a role in the initial adhesion and rolling of platelets and leukocytes to areas of injury and inflammation via its ligand P-selectin glycoprotein ligand 1 (PSGL-1) (Frenette et al 2000). By binding to P-selectin on the surface of endothelial cells and platelets, crizanlizumab has been shown to effectively block interactions between endothelial cells, platelets, sickled red blood cells and leukocytes. The pharmacological effect of interfering with P-selectin/PSGL-1 interactions is anti-inflammatory. Considering the cell-cell interactions that are mediated by P-selectin binding, crizanlizumab may have immunosuppressant properties.

The rationale for investigating crizanlizumab in MF patients is based on studies demonstrating a potential role for P-selectin in MF pathophysiology. PMF has a unique cellular signature: both bone marrow (BM) and the spleen contain numerous megakaryocytes (MK) exhibiting distinctive abnormalities that include reduced expression of the transcription factor Gata1 (Vannucchi et al 2005), increased proliferation with delayed maturation (Centurione et al 2004, Schmitt et al 2000) and PMF MKs also express increased levels of P-selectin (Schmitt et al 2000).

PMF MK engage in emperipolesis with neutrophils, which in the case of PMF, may lead to MK para-apoptosis (Centurione et al 2004, Thiele et al 1997) that may cause release of transforming growth factor beta (TGFβ) to the microenvironment (Zingariello et al 2013). In agreement with this hypothesis, it has been found that plasma from PMF patients contains significantly increased levels of total and bioactive TGFβ than normal (Zingariello et al 2013). The relevance of these MKs and TGFβ abnormalities in the pathogenesis of PMF was shown in mice where the reduction of Gata1 expression in MK by ablation of its lineage-specific enhancer (hypomorphic Gata1low mutation Shivdasani et al 1997) induced MK abnormalities similar to those observed in PMF (Centurione et al 2004, Vannucchi et al 2002, Vyas et al 1999). This included an increase of the plasma levels of TGFβ, and the formation of a myelofibrosis phenotype. In addition, deleting the P-selectin gene in the myelofibrosis mouse model carrying the hypomorphic Gata1low mutation that induces megakaryocyte abnormalities, resulted in substantial reduction of MF disease burden in mice. P-selnullGata1low mice survived splenectomy and lived 3 months longer than P-selWTGata1low littermates, and they expressed only limited fibrosis in the bone marrow or splenomegaly (Spangrude et al 2016). Deletion of P-selectin also disrupted megakaryocyte/neutrophil interactions in the spleen, reduced TGF-β content, and corrected the hematopoietic stem cells (HSC) distribution that in Gata1low mice, as in PMF patients, is abnormally expanded in the spleen.

A recent study demonstrated that P-selectin expression is increased in JAK2V617F endothelial cells from *Pdgfb-iCreERT2; JAK2$^{V617F/WT}$* mice (Guy et al 2019). The increased P-selectin expression at the endothelial cell (EC) surface are a pro-adhesive phenotype of JAK2^{V617F} EC. Pre-treatment of mice with the P-selectin blocking antibody completely abrogated thrombus formation in *Pdgfb-iCreERT2; JAK2$^{V617F/WT}$* mice, but had no effect in control mice. Furthermore, JAK2^{V617F} human umbilical vein endothelial cells (HUVEC) when treated in vitro in the presence of a P-selectin blocking antibody, showed a complete reversion of the hyper-adhesive properties of JAK2^{V617F} HUVEC. The results of this study demonstrated that the pro-thrombotic phenotype of JAK2^{V617F} EC is primarily the consequence of increased adhesive properties, due to overexpression of membrane P-selectin.

Conversely, pharmacological inhibition of TGFβ reduced P-selectin expression in MKs and corrected HSC distribution. Spleens, but not marrow of Gata1low mice contained numerous cKITpos activated fibrocytes, probably of dendritic cell origin, whose membrane protrusions interacted with MKs establishing niches hosting immature cKITpos hematopoietic cells. These activated fibrocytes were not detected in spleens from P-selnullGata1low or TGFβ-inhibited Gata1low littermates but were observed in spleen, but not in marrow, from PMF patients. Therefore, in Gata1low mice, and possibly in PMF, abnormal P-selectin expression in MKs may mediate the pathological cell interactions that increase TGFβ content in MKs and favor the establishment of a microenvironment that supports myelofibrosis-related HSC in spleen (Spangrude et al 2016).Based on these findings, pharmacologic neutralization of P-selectin on MKs via a monoclonal antibody holds promise to prevent progression and bone marrow fibrosis in MF patients.

P-selectin also plays a pivotal role in the pathophysiology of sickle cell disease (SCD) and crizanlizumab was recently approved in the USA as Adakveo® to reduce the frequency of vaso-occlusive crises (VOCs), or pain crises, in adult and pediatric patients aged 16 years and older with SCD. Additional studies in SCD patients (CSEG101A2201 and CSEG101A2202) have helped identify an important feature of crizanlizumab *in vitro.*

It was found that there was interference with laboratory tests that measure the amount of platelets in blood in SCD patients treated with crizanlizumab. Clinical and pre-clinical data suggest this is an ex vivo phenomenon (laboratory test interference), that is ETDA- and time-dependent, without indication of platelet clumping in vivo, and has no influence on the safety of crizanlizumab. Further information and recommendations that may mitigate this laboratory test interference are provided in Section 8.4.1.

Detailed information about crizanlizumab safety and efficacy is provided in the Investigator's Brochure.

1.1.2.4 Sabatolimab: an inhibitor of a negative immune regulator, TIM-3

Sabatolimab (MBG453) is a high-affinity, ligand-blocking, humanized anti-T-cell immunoglobulin domain and mucin domain-3 (TIM-3) IgG4 antibody. It is a novel checkpoint inhibitor that blocks the binding of an immune checkpoint receptor TIM-3 to phosphatidylserine (PtdSer).

Immune checkpoints refer to a variety of inhibitory pathways that are crucial for maintaining self-tolerance and modulating the duration and amplitude of physiological immune responses in peripheral tissues in order to minimize collateral tissue damage (Shin and Ribas 2015).

Checkpoint inhibitors, such as ipilimumab targeting CTLA-4, pembrolizumab and nivolumab targeting programmed cell death protein 1 (PD-1), have been approved for numerous cancer indications including hematologic malignancies.

TIM-3 is expressed on the majority of CD34+CD38- leukemic stem cells (LSCs) and CD34+CD38+ leukemic progenitors in Acute Myeloid Leukemia (AML), but not on CD34+CD38- normal HSCs (Jan et al 2011, Kikushige et al 2010). Functional evidence for a key role for TIM-3 in AML was established by use of an anti-TIM-3 antibody which inhibited engraftment and development of human AML in immunodeficient murine hosts (Kikushige et al 2010). Upregulation of TIM-3 is also associated with leukemic transformation of pre-leukemic disease, include myelodysplastic syndromes (MDSs) and myeloproliferative neoplasms (MPNs), such as chronic myelogenous leukemia (CML) (Kikushige et al 2015). TIM-3 expression on MDS blasts was also found to correlate with disease progression (Asayama et al 2017).

In addition to its cell-autonomous role on pre-leukemic and leukemic stem cells, TIM-3 has a widespread and complex role in immune system regulation, with published roles in both the adaptive immune response (CD4+ and CD8+ T effector cells, regulatory T cells) and innate immune responses (macrophages, dendritic cells, natural killer cells) (Ndhlovu et al 2012, Anderson et al 2007). TIM-3 has a critical role in tumor-induced immune suppression as it marks the most suppressed or dysfunctional populations of CD8+ T cells in animal models of solid and hematologic malignancies (Yang et al 2012, Zhou et al 2011, Sakuishi et al 2010) and is expressed on FoxP3+ regulatory T cells (Tregs), which correlate with disease severity in many cancer indications (Yan et al 2013, Gao et al 2012). Blockade of TIM-3 on macrophages and antigen cross-presenting dendritic cells enhances activation and inflammatory cytokine/chemokine production (de Mingo Pulido et al 2018, Zhang et al 2012, Chiba et al 2012, Zhang et al 2011), ultimately leading to enhanced effector T cells responses.

Sabatolimab has been evaluated as a single agent or in combination with PDR001 (an anti-PD IgG4 Ab currently in the clinic) in a first in human (CMBG453X2101) clinical trial in solid tumors. It is also being investigated in a phase Ib study (CPDR001X2105) as a single agent or in combination with PDR001 and/or decitabine in patients with AML and patients with high risk MDS.

Detailed information about sabatolimab safety and efficacy is provided in the Investigator's Brochure.

1.1.2.5 Rineterkib: a potent and selective ERK1/2 kinase inhibitor

Rineterkib is a potent, selective, orally bioavailable, adenosine triphosphate (ATP)-competitive, inhibitor of Extracellular signal-regulated kinase 1 (ERK1) and Extracellular signal-regulated kinase 2 (ERK2).

In vitro, rineterkib demonstrated potent anti-proliferative activity (with sub-µM half maximum inhibitory concentration (IC_{50})) in cell lines containing mutations that activate mitogen-activated protein kinase (MAPK) pathway signaling, including mutations of v-raf Murine

Sarcoma Viral Oncogene Homolog B1 (*BRAF*), Kirsten rat sarcoma viral oncogene homolog (*KRAS*), Neuroblastoma RAS viral (v-ras) oncogene homolog (*NRAS*) and mitogen-activated protein kinase kinase 1 (*MEK1*). Rineterkib also effectively inhibited the proliferation of the A-375 melanoma cell line and its engineered derivatives expressing multiple known molecular drivers of BRAF and/or MEK inhibitor resistance, including $BRAF^{V600E}$, $BRAF^{p61V600E}$, $NRAS^{Q61K}$, $MEK1^{C121S}$, $MEK1^{E203K}$, $MEK1^{P124L}$, $MEK1^{Q56P}$ and $MEK2^{Q60P}$.

In *in vivo* human tumor xenograft models, rineterkib demonstrates a pharmacokinetic (PK)/pharmacodynamics (PD)/efficacy relationship, leading to dose-dependent tumor growth inhibition and regression when dosed either daily or intermittently in human Non-Small Cell Lung Carcinoma (NSCLC) Calu-6 ($KRAS^{Q61K}$), ovarian Hey-A8 ($KRAS^{G12D}$/$BRAF^{G464E}$) and melanoma A-375 ($BRAF^{V600E}$) xenograft models. Rineterkib has been evaluated as a single agent in a first in human study (CLTT462X2101), to establish the safety and tolerability of rineterkib in adult patients with advanced solid tumors harboring MAPK pathway alterations. It is currently being investigated in a Phase Ib study (CLXH254X2102) in combination with LXH254 (BRAF and CRAF inhibitor) in adult patients with advanced or metastatic KRAS or BRAF mutant Non-Small Cell Lung Cancer or NRAS mutant melanoma. It is also being investigated in combination with dabrafenib (DRB436) as part of a platform study in adult patients with advanced or metastatic BRAF V600 colorectal cancer (ADPT01C12101). Detailed information about rineterkib safety and efficacy is provided in the Investigator's Brochure.

1.1.2.6 NIS793: an anti-TGFβ monoclonal antibody

NIS793 is a recombinant human immunoglobulin G2 (IgG2) monoclonal antibody (mAb) that binds to TGFβ1 and TGFβ2 with high affinity and to TGFβ3 with lower affinity. Consistent with the binding affinities, NIS793 displayed potent TGF□1- and TGF□2-neutralizing activity, while less effect was observed against TGFβ3. Administration of NIS793 significantly reduced tumor growth in immunodeficient mouse models.

Preclinical studies support a pathobiological role of TGFβ in MF (Schmitt et al 2002, Vannucchi et al 2005, Wang et al 2006). Additionally, Vannucchi et al. 2005 showed that in both TPO^{high} mice and GATA-1^{low} mice development of myelofibrosis was associated with high TGFβ1 content in extracellular fluids of marrow and spleen.

For the non-clinical toxicology of NIS793, refer to NIS793 Investigator's Brochure. Briefly, before the first entry in humans, NIS793 was investigated in tissue cross-reactivity studies and in a 13-week rat toxicity study up to 10mg/kg/wk i.v. as well as in a 4-week cynomolgus monkey toxicity study up to 16mg/kg/wk i.v. both followed by 4-week recovery period. In the rat, minimal to mild non-adverse effects were observed in liver, kidney, bone, and eyelids, which could reflect inhibition of the tissue homeostatic effects of TGFβ with NIS793 (bone, eyelids). For the effects in liver and kidney, the relation to treatment and inhibition of TGFβ is not clear and could indicate incidental findings or an increase in normal rat specific background findings. In the monkey study, assessments of safety pharmacology endpoints were included. No adverse effects on cardiovascular, central nervous system or respiratory function were observed. Overall, no observed adverse event level (NOAEL) were set to 10mg/kg in the rat study and to 16mg/kg in the cynomolgus study.

In a rat non-GLP pharmacology model of lung fibrosis, valvulopathy in the heart was found at NIS793 at 30mg/kg intraperitoneal, every second day (IP, Q2D) after 14 days. The exposure levels in these animals were in the clinically relevant range. In currently evaluated 8-week dose range finding and tolerability studies in rats and monkeys, adverse findings were observed in the kidney (tubulo-interstitial nephritis with tubular hypertrophy/hyperplasia) and the vascular system (vascular inflammation, vascular necrosis and endothelial cell hyperplasia) of cynomolgus monkeys at 65 mg/kg/wk i.v., and in the heart (cardiac valvulopathy) of rats at 30 and 90 mg/kg/wk i.v. Toxicokinetic and anti-drug antibody data are not yet available. Based on modeling and simulation projections of exposure in rats and monkeys, these findings likely occurred at exposure comparable to those achieved in participants in current oncology and hematology trials.

An investigator-initiated study (registered at www ClinicalTrials gov under NCT01291784) to investigate the tolerability and safety of GC1008 (Fresolimumab; Genzyme) a human immunoglobulin (IgG4) kappa monoclonal antibody capable of neutralizing TGFβ1, TGFβ2 and TGFβ3 in patients with PMF or post-PV/ET MF showed evidence of a clinical response based on standard criteria and thus indicates the likelihood that targeting TGFβ with monoclonal antibodies or small molecule inhibitors is a promising strategy for treating patients with MF (Mascarenhas et al 2014). Another phase I/Ib study is currently ongoing to assess the safety and tolerability of another compound (AVID200) that targets TGFβ1 and TGFβ3 in patients with PMF or post-PV/ET MF (registered at www ClinicalTrials gov under NCT03895112).

TGFβ1 is the best characterized pro-fibrotic factor within the family. TGFβ2 also displays potent fibrotic activity, whereas TGFβ3 appears to have anti-fibrotic activity in some tissues (Walton et al 2017). The selectivity of NIS793 for TGFβ1 and TGFβ2 over TGFβ3 could be a great advantage to inhibit fibrosis especially when combined with ruxolitinib.

NIS793 has been evaluated in one clinical study to date, this first in human study (CNIS793X2101) is a dose escalation study of NIS793 in combination with PDR001 in adult patients with advanced malignancies. It is also being investigated in combination with SOC chemotherapy in first line metastatic pancreatic ductal adenocarcinoma (mPDAC), metastatic colorectal adenocarcinoma and lower risk myelodysplastic syndrome.

Detailed information about NIS793 safety and efficacy is provided in the Investigator's Brochure.

1.2 Purpose

MF is defined by progressive bone marrow fibrosis, the result of a nonclonal fibroblastic response to inflammatory and fibrogenic cytokines produced by aberrant clonal myeloid cells, most prominently megakaryocytes. This disruption of the medullary erythropoietic niche is the primary mechanism governing the bone marrow failure and anemia, which typify MF. Anemia is among the cardinal features of MF. Nearly 40% of MF patients have hemoglobin (Hb) levels < 10 g/dL at diagnosis, and nearly one-quarter already need red blood cell (RBC) transfusions. All patients with MF will eventually develop anemia, which has consistently been associated with inferior QoL measures. Furthermore, anemia is the disease feature most consistently associated with poor prognosis in MF (Naymagon and Mascarenhas 2017).

Ruxolitinib demonstrated improvements in splenomegaly and constitutional symptoms, presumed to be mediated by its anti-proliferative effects, and through normalization of cytokine signaling, as abnormal cytokine levels have been associated with MF symptoms. However, not all patients respond to ruxolitinib, with some losing response while on treatment, and some having to discontinue treatment owing to toxicities (Verstovsek et al 2017).

Ruxolitinib does not improve cytopenias but may aggravate anemia due to transient suppression of the erythropoiesis, which at least partially resolves over time on continuous therapy. Current treatment options for these patients are limited in their efficacy, durability and tolerability. Anemia and thrombocytopenia have remained challenges in the management of MF and represent a high unmet medical need.

Combination therapies of ruxolitinib with novel agents may deliver transformational clinical benefits such as improvement of PFS as a consequence of superior disease control or reduction of the malignant clone, associated with an improvement of cytopenia and in particular anemia, as well as improvement in QoL as captured by relevant patient reported outcomes measurements (PROs).

The purpose of this study is to investigate the safety, pharmacokinetics and preliminary efficacy of combinations treatment of ruxolitinib with five novel compounds: siremadlin, crizanlizumab, sabatolimab, rineterkib and NIS793 in MF subjects. The study was planned in three parts, as described in Section 3:

- Part 1: Dose escalation and safety run-in (recommended Phase II dose confirmation)
    - Core treatment phase
    - Extension treatment phase

  Part 1 refers now to the core treatment phase unless specified.
- Part 2: Selection
- Part 3: Expansion

Part 1 corresponds to phase Ib and Parts 2 and 3 correspond to phase II.

The purpose of the extension treatment phase is to provide continued drug access to ongoing subjects who are deriving clinical benefit.

2 Objectives and endpoints

Please refer to Section 8.3 for details on the endpoint and to Section 12 for details on the analysis.

As the enrollment was permanently halted, not all planned study objectives for Parts 1, 2, and 3 could be completed. All Parts 2 and 3 objectives will not be pursued. [redacted]

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the preliminary efficacy of each novel ruxolitinib combination treatment arm (Parts 2 & 3)	• Response rate (RR) for the composite endpoint (anemia improvement of ≥ 1.5 g/dL and no spleen volume progression and no symptom worsening) at the end of Cycle 8 for all arms containing NIS793 or Cycle 6 for all other arms.
• To characterize the safety, tolerability, and recommended phase 2 dose (RP2D) of each combination partner used with ruxolitinib (Part 1)	• Incidence and severity of dose limiting toxicity (DLTs) within the first 2 treatment cycles in Part 1 of the study
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the proportion of subjects in each treatment arm who achieve an Hb improvement of ≥ 2.0 g/dL or ≥ 1.5 g/dL (Parts 2 & 3)	• Proportion of subjects achieving improvement of Hb level of ≥ 1.5 g/dL from baseline • Proportion of subjects achieving improvement of Hb level of ≥ 2.0 g/dL from baseline
• To evaluate changes in symptoms of myelofibrosis in each treatment arm using MFSAF v4.0 and EORTC QLQ-C30 patient reported outcomes (PROs) (Parts 2 & 3)	• Change in MFSAF v4.0 and EORTC QLQ-C30 from baseline, including proportion of subjects who achieved at least 50% reduction from baseline in MFSAF v4.0 Total Symptom Score (TSS) at the end of Cycle 4 (NIS793 arms) or Cycle 3 (all other arms), of Cycle 8 (NIS793 arms) or Cycle 6 (all other arms) and of Cycle 16 (NIS793 arms) or Cycle 12 (all other arms) from baseline.
• To evaluate changes in symptoms of myelofibrosis in each treatment arm using MFSAF v4.0 (Part 1)	• Change in MFSAF v4.0 from baseline, including proportion of subjects who achieved at least 50% reduction from baseline in MFSAF v4.0 Total Symptom Score (TSS) at the end of Cycle 4 (NIS793 arms) or Cycle 3 (all other arms), of Cycle 8 (NIS793 arms) or Cycle 6 (all other arms) and of Cycle 16 (NIS793 arms) or Cycle 12 (all other arms) from baseline.
• To characterize the pharmacokinetic profile of ruxolitinib administered in combination with siremadlin, crizanlizumab, sabatolimab, rineterkib and NIS793, respectively (Parts 1, 2 & 3)	• PK parameters (e.g., AUC, Cmax, Tmax) and concentration vs. time profiles of each investigational drug with in combination regimens
• To assess emergence of anti-crizanlizumab, anti-sabatolimab, or anti-NIS793 antibodies following one or more IV infusions (Parts 1, 2 & 3)	• Presence and/or concentration of anti-crizanlizumab, anti-sabatolimab or anti-NIS793 antibodies
• To evaluate the changes in spleen size in each treatment arm (Part 1 core and extension, Parts 2 & 3)	• Change in spleen length (by palpation) from baseline. • Change in spleen volume (by MRI/CT) from baseline, including proportions of subjects who achieved (i) at least 35% spleen volume reduction and (ii) at least 25% spleen volume reduction at the end of Cycle 8 (NIS793 arms) or Cycle 6 (all other arms) from baseline and, at the end of Cycle 16 (NIS793 arms) or Cycle 12 (all other arms) from baseline respectively.
• To evaluate the effect of each ruxolitinib combination treatment in delaying progression of MF and estimate time to	• Estimate of progression free survival (PFS) where events are defined as follows: • Progressive splenomegaly as assessed by increasing spleen volume (by MRI/CT) of ≥ 25% from baseline.

Objective(s)	Endpoint(s)
progression free survival (PFS) event (Parts 2 & 3)	The progression date will be the date of MRI/CT assessment confirming spleen volume increase of ≥ 25% from baseline • Accelerated phase defined by a circulating peripheral blood blast content of > 10% but < 20% confirmed after 2 weeks. The progression date will be the date of first increase in peripheral blood blast content of > 10% • Deteriorating cytopenia (dCP) independent from treatment defined for all patients by platelet count < 35 x10^9/L or neutrophil count < 0.75 x 10^9/L that lasts for at least 4 weeks. The progression date will be the date of first decrease of platelets < 35 x10^9/L or neutrophils < 0.75 x 10^9/L confirmed after 4 weeks • Leukemic transformation defined by a peripheral blood blast content of ≥ 20% associated with an absolute blast count of ≥ 1x10^9/L that lasts for at least 2 weeks or a bone marrow blast count of ≥ 20%. The progression date will be the date of first increase in peripheral blood blast content of ≥ 20% associated with an absolute blast count of ≥ 1x10^9/L OR the date of the bone marrow blast count of ≥ 20% • Death from any cause
• To evaluate the effect on bone marrow fibrosis in each treatment arm (Parts 2 & 3)	• Proportion of subjects achieving improvement in bone marrow fibrosis of ≥ 1 grade from baseline
• To evaluate long-term safety and tolerability of ruxolitinib combination treatments in each arm (Part 1 coreand extension, Parts 2 & 3)	• Frequency, duration and severity of adverse events, abnormalities in vital signs and laboratory test values, including ECG data

[redacted]

3 Study design

This is an open-label, multi-center, three-part, phase Ib/II open platform study to assess safety and efficacy of ruxolitinib in combination with novel compounds in myelofibrosis patients followed by an extension treatment phase in Part 1.

The study was planned in three parts. In the context of the permanent enrollment halt, the study design has been revised as follows:

- Part 1: Dose escalation and safety-run-in (recommended Phase II dose confirmation) including a core and an extension treatment phase
- Part 2: Selection (unchanged as the only randomized subject has discontinued prior to amended protocol version 08)
- Part 3: Expansion (not applicable as it will never be initiated)

After a screening period of up to 28 days (Day -28 to Day -1), eligible subjects will begin treatment on Cycle 1 Day 1 (C1D1) and will be treated for a planned duration of 24 weeks, which is 8 cycles for all treatment arms containing NIS793 or 6 cycles for all other treatment arms in Part 1, or for a planned duration of 48 weeks, which is 16 cycles for all arms containing NIS793 and 12 cycles for all other arms in Parts 2 and 3, per the treatment arms outlined below for each part of the study. Subjects may be discontinued from treatment earlier due to unacceptable toxicity, disease progression or treatment is discontinued at the discretion of the investigator or the subject. Refer to Section 8 for details on the screening period, treatment period and assessments, and to Section 9 for details on-study discontinuation and completion.

Assuming all five combination treatments enter Part 2 and one combination treatment is expanded in Part 3, a total of approximately 240 subjects are expected to be enrolled in all three parts of the study: approximately 50 subjects in Part 1; approximately 155 subjects in Part 2; and approximately 35 subjects in Part 3. If additional combination treatments are expanded in Part 3, then the sample size will increase by approximately 35 subjects per treatment combination, to a maximum of approximately 175 subjects in Part 3, resulting in a maximum of approximately 380 subjects in all 3 parts of the study.

Crossover, re-allocation or re-randomization of subjects to other combination arms including better performing arms within the same Part of the study is not permitted. Subjects are permitted to participate in another Part of the study, if all corresponding inclusion and none of the exclusion criteria are met, provided they are not randomized twice. This means that Part 1 subjects could join Part 2 or Part 3 of the study and Part 2 and Part 3 subjects could participate in Part 1 of the study only. However, Part 2 subjects are not allowed to join Part 3 and vice versa.

An overview of the study design is shown in Figure 3-1. A hypothetical example illustrating interim analyses in Part 2 and primary analysis of Part 3 is shown in Section 16.8 (Appendix 8).

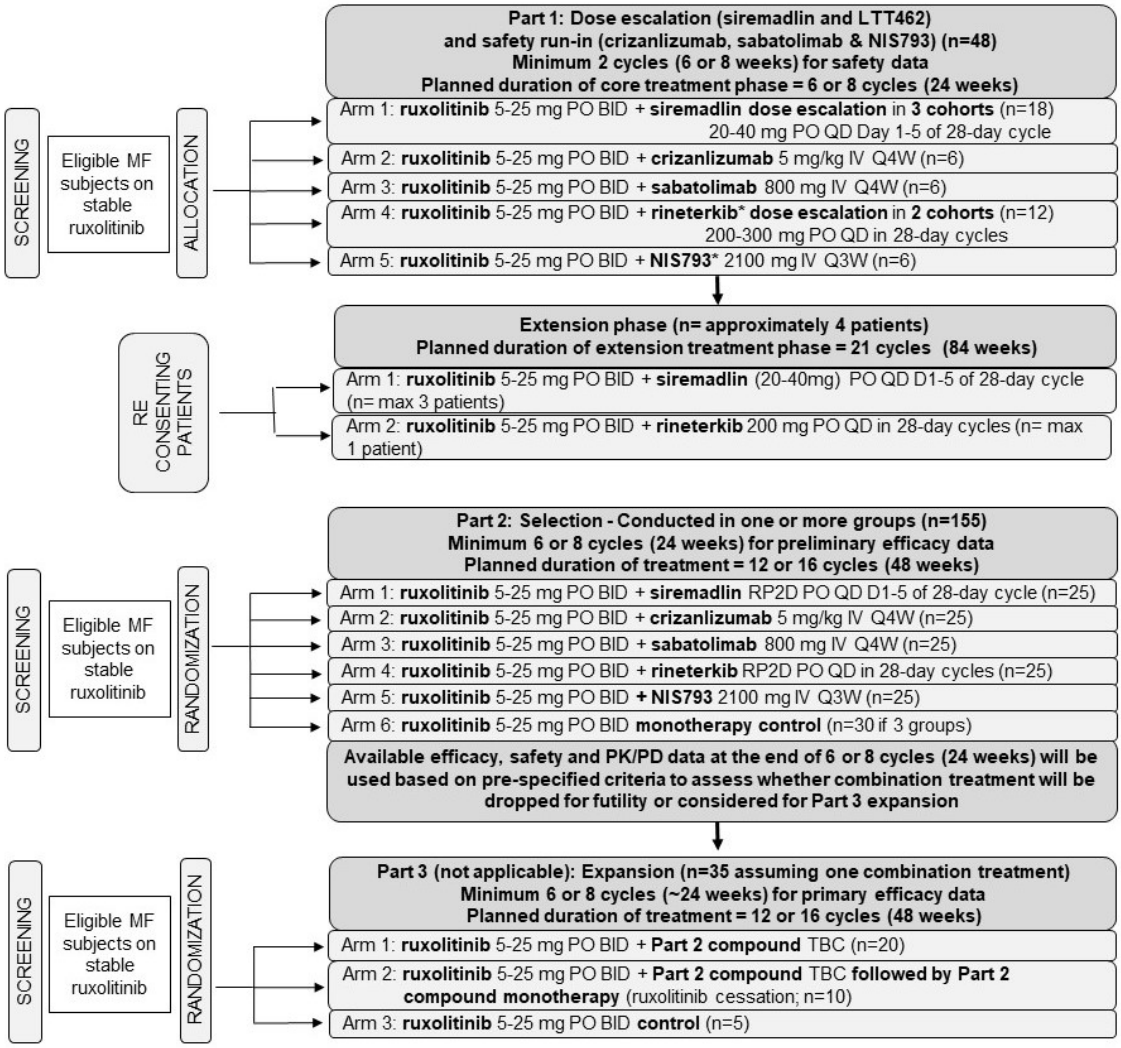
In the context of the permanent enrollment halt, the study design is revised as follows:

- Part 1 is updated to define a core treatment phase and add an extension treatment phase. The end of core treatment phase will occur when amended protocol version 08 is implemented, after a minimum of 24 weeks in the core treatment phase. The extension treatment phase will occur (for ongoing subjects meeting eligibility criteria who are re-

consented) from the time when amended protocol version 08 is implemented until the end of extension study treatment.

- Part 2 is not updated.
- Part 3 is not applicable as it will never be initiated.

Figure 3-1 Overview of study design



*Rineterkib and NIS793 added in amendment 4 of the protocol

TBC: To be confirmed

Notes:

Part 2 will be conducted in groups and will consist of a maximum of 5 arms of combination treatment plus a ruxolitinib monotherapy control arm. Each group consists of 1 or more combination treatments. A ruxolitinib monotherapy arm will open with the start of Part 2. The number of arms will depend on the results of the Part 1 dose escalation and safety run-in phase. There will be a maximum of approximately 155 subjects in total in Part 2 if all 5 combination treatments enter Part 2. Part 3 will consist of 3 arms per treatment combination that is expanded

with approximately 35 subjects in total per treatment combination. If additional treatment combinations are continued to be investigated in Part 3, then there will be up to a maximum of 175 subjects in Part 3 (i.e., 35 subjects x 5 combination treatments).

Assuming all 5 combination treatments enter Part 2 and one combination treatment enters Part 3, then there will be approximately 240 subjects enrolled in all three parts of the study.

As the enrollment was permanently halted, the only randomized subject in Part 2 has discontinued prior to amended protocol version 08, and Part 3 will not be initiated, therefore the description below for Parts 2 and 3 are not applicable.

Part 1: Dose escalation and safety run-in

The primary objective of the first part of the study is to characterize safety, tolerability, and the recommended Phase 2 dose (RP2D) of novel agents given in combination with ruxolitinib in subjects with myelofibrosis.

For siremadlin, since there are overlapping toxicities with ruxolitinib, a dose escalation will be performed to determine the RP2D of the combination treatment with ruxolitinib. It is estimated that approximately 18 subjects will be included in the dose escalation part for the combination of ruxolitinib and siremadlin.

For rineterkib a dose escalation will also be performed to determine the RP2D of the combination treatment with ruxolitinib. It is estimated that approximately 12 subjects will be included in the dose escalation part of the combination of ruxolitinib with rineterkib. For crizanlizumab, sabatolimab, and NIS793 the proposed RP2D is known prior to the study start and based on previous single agent phase I and phase II studies in solid and hematologic malignancies. These compounds are monoclonal antibodies and no overlapping toxicities with ruxolitinib are expected (see Section 4.2.2, Section 4.2.3, and Section 4.2.5). However, since it is the first time these compounds will be given in combination with ruxolitinib and also the first time in an MF patient population, a safety run-in based on approximately 6 subjects will be conducted for these combination arms. The safety run-in is performed to assess the risk of unexpected toxicities, to confirm [redacted] pharmacokinetic properties, and to assess potential drug-drug interactions (DDI). In case of unexpected toxicities, administration of crizanlizumab, sabatolimab or NIS793 will be interrupted or terminated.

The core treatment phase of Part 1 will include the following five combination arms, one novel agent per arm in combination with stable ruxolitinib.

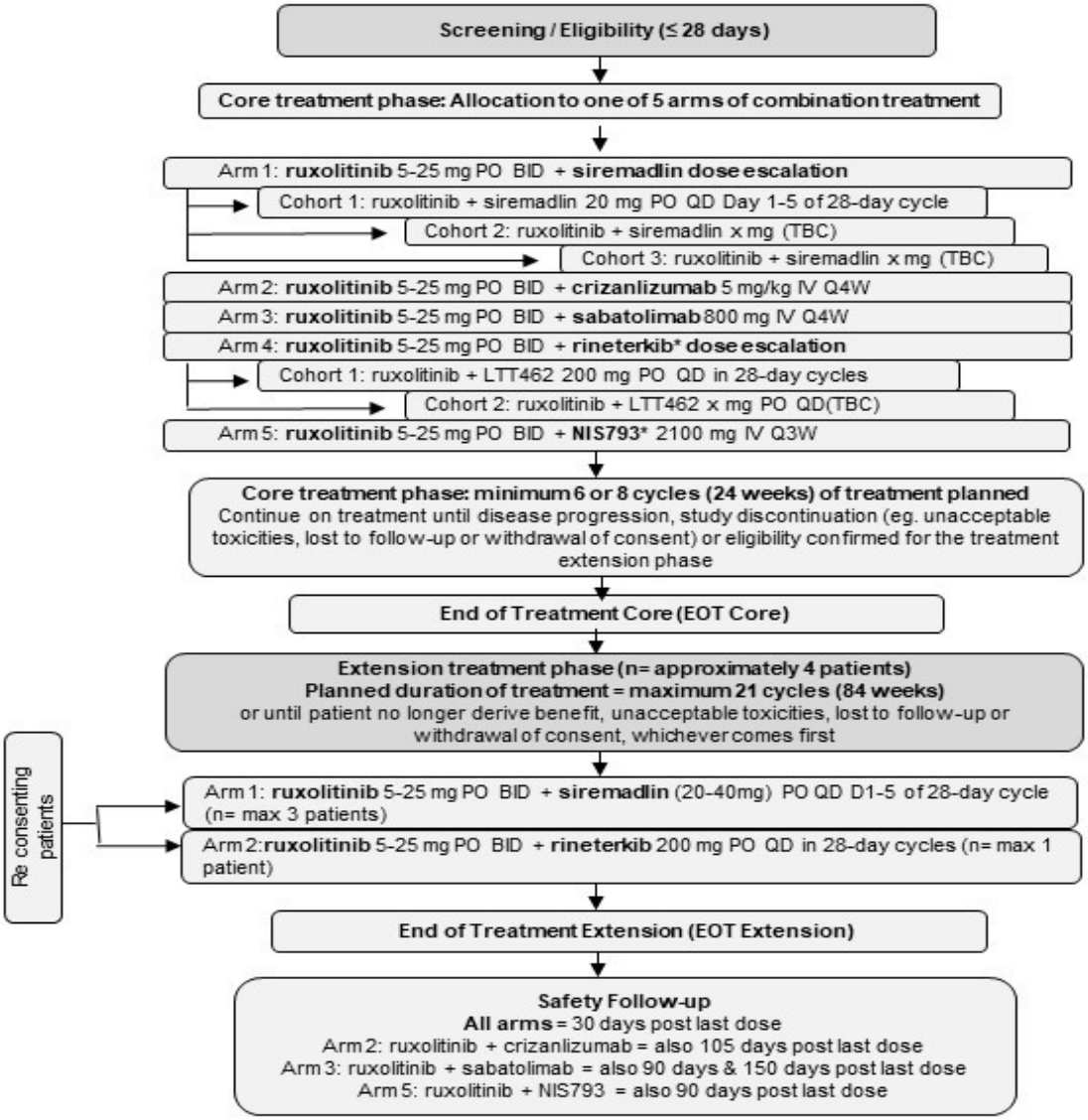
- Arm 1: Ruxolitinib 5-25 mg PO BID and siremadlin at various dose levels (either 10 mg, 20 mg (starting dose), 30 mg or 40 mg) PO QD on Days 1 to 5 of a 28-day cycle
- Arm 2: Ruxolitinib 5-25 mg PO BID and crizanlizumab 5 mg/kg IV once every 4 weeks (Q4W) with an additional loading dose administered at Cycle 1 Day 15 (C1D15)
- Arm 3: Ruxolitinib 5-25 mg PO BID and sabatolimab 800 mg IV Q4W
- Arm 4: Ruxolitinib 5-25 mg PO BID and rineterkib at various dose levels (either 100 mg, 200 mg (starting dose) or 300 mg) PO QD in 28-day cycles
- Arm 5: Ruxolitinib 5-25 mg PO BID and NIS793 2100 mg IV Q3W

The dose of ruxolitinib for all subjects should not change from the stable dose used prior to first dose of study treatment. As the combination arm of ruxolitinib and siremadlin in Part 1 is likely to enroll more subjects overall to evaluate various dose levels of siremadlin with ruxolitinib, eligible subjects will initially be allocated to the first dosing cohort of the ruxolitinib and siremadlin arm until enrolment of the first cohort is complete. Eligible subjects will then be allocated to either the ruxolitinib + crizanlizumab arm, the ruxolitinib + sabatolimab arm, the first cohort of the ruxolitinib + rineterkib arm, the ruxolitinib + NIS793 arm or subsequent cohorts of the ruxolitinib + siremadlin arms, and the ruxolitinib + rineterkib arm, as appropriate. The assignment of a subject to a particular treatment arm and dose cohort will be using the interactive response technology (IRT) system and coordinated by Novartis.

Patients who have received study treatment in the Part 1 core treatment phase for a minimum of 24 weeks and are benefitting from the combination treatment may be eligible to enter the extension treatment phase after amended protocol version 08 is implemented (see Section 5.3).

An overview of the study design at the subject level in Part 1 is shown in Figure 3-2.

Figure 3-2 Overview of study design at subject level in Part 1



*Rineterkib and NIS793 added in amendment 4 of the protocol

TBC: To be confirmed

The combination treatment arms eligible for Part 2 will be determined after the Data Monitoring Committee (DMC) and Novartis study personnel have reviewed all of the available relevant data. This will include, but not limited to, safety information, DLTs, available [redacted], PK and PD data from evaluable subjects in Part 1 who have completed a minimum of 2 cycles of treatment or discontinued from the study in each treatment arm.

This study is an open platform design as outlined in Section 4.1. Thus, new suitable combination treatments with ruxolitinib may be added to the protocol by amending the protocol. The potential adjustments to the design triggered by adding new treatments will be discussed in a protocol amendment.

Part 2: Selection

Part 2 of the study for each combination treatment will start once sufficient information has been collected in Part 1 of the study to assess the safety and tolerability of the novel agents in combination with ruxolitinib and to make an informed decision on which arms will be studied in Part 2. Combination treatment arms may enter Part 2 in a staggered manner. The primary objective of Part 2 is to evaluate the preliminary efficacy of ruxolitinib in combination with novel agents in subjects with myelofibrosis. Eligible subjects will be randomized to one or more combination treatment arm(s) or a ruxolitinib monotherapy arm within one or more groups. The combination arms will be selected based on the results from Part 1, as follows:

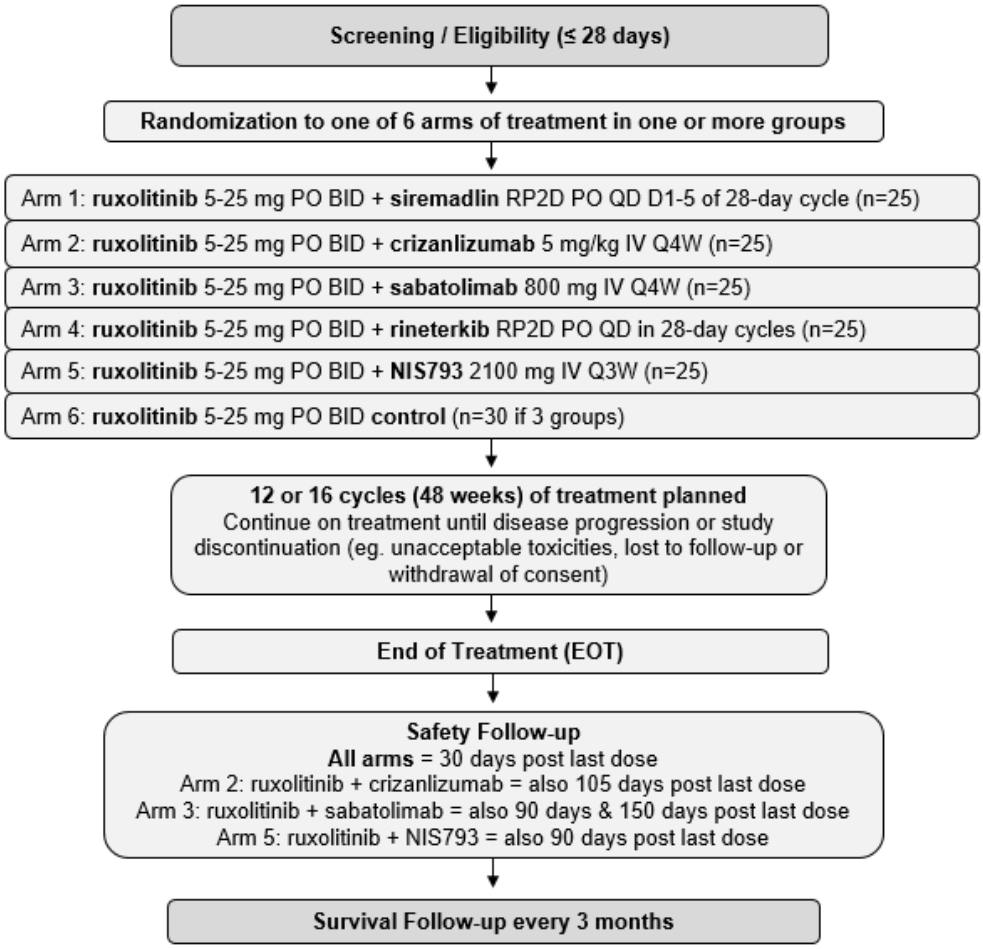
- Arm 1: Ruxolitinib 5-25 mg PO BID and siremadlin at the RP2D from Part 1 PO on Days 1 to 5 of a 28-day cycle
- Arm 2: Ruxolitinib 5-25 mg PO BID and crizanlizumab 5 mg/kg IV Q4W with addition of a loading dose administered at C1D15
- Arm 3: Ruxolitinib 5-25 mg PO BID and sabatolimab 800 mg IV Q4W
- Arm 4: Ruxolitinib 5-25 mg PO BID and rineterkib at the RP2D from Part 1 PO QD in 28-day cycles
- Arm 5: Ruxolitinib 5-25 mg PO BID and NIS793 2100 mg IV Q3W
- Arm 6: Ruxolitinib 5-25 mg PO BID monotherapy control

The dose of ruxolitinib for all subjects should not change from the stable dose used prior to enrolment into the study.

As the enrollment was permanently halted, the only randomized subject in Part 2 has discontinued prior to amended protocol version 08, therefore the description below for Part 2 is not applicable.

Approximately 25 subjects will be randomized to each combination treatment arm, and approximately 30 subjects will be randomized to the common ruxolitinib monotherapy control arm assuming 3 groups are opened. Subjects will be randomized using the IRT system and treatment will continue for at least 16 cycles for treatment arms with NIS793 or 12 cycles for all other treatment arms (48 weeks). An overview of the study design at the subject level in Part 2 is shown in Figure 3-3.

Figure 3-3 Overview of study design at subject level in Part 2



Notes:

Part 2 will consist of a maximum of 5 arms of combination treatment plus a ruxolitinib monotherapy control arm. The number of combination treatment arms will depend on the results of the Part 1 dose escalation and safety run-in phase. There will be up to approximately 155 subjects in total in Part 2, including the ruxolitinib comparator arm.

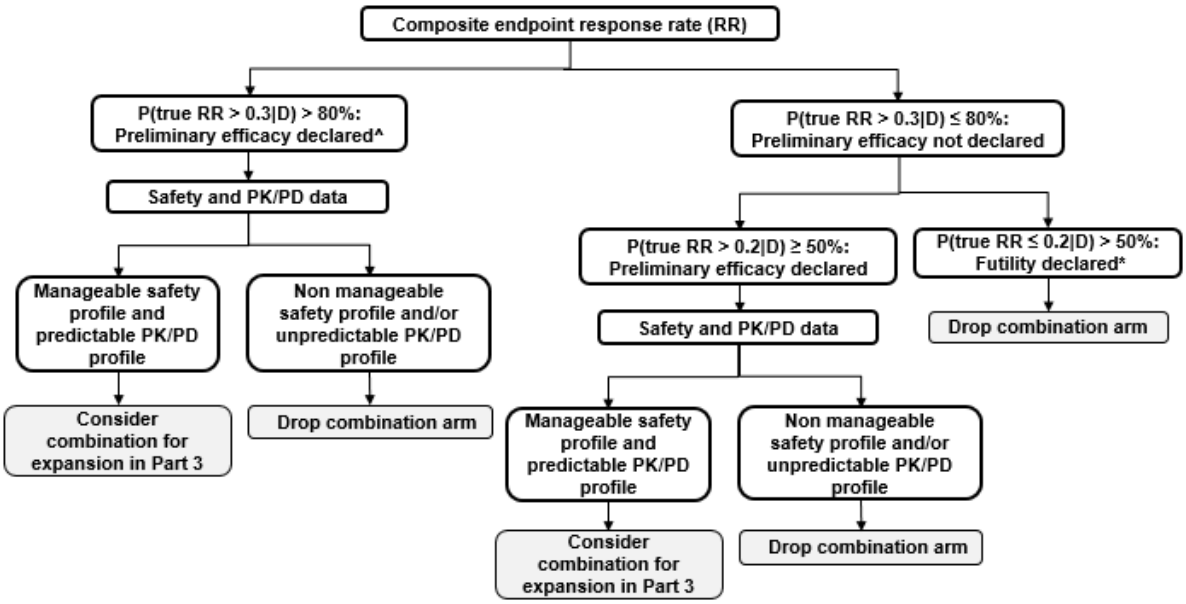
Part 2 will be conducted in one or more groups. Each group consists of one or more combination treatments along with a common ruxolitinib monotherapy control arm.

Two interim analyses are planned for each combination treatment in Part 2 to expand into Part 3. The first interim analysis will be conducted after at least 10 subjects per combination treatment arm in Part 2 have completed 8 cycles (arms with NIS793) or 6 cycles (all other arms) of treatment. A threshold for outstanding preliminary efficacy will be applied to the combination treatments in this interim analysis. An arm that crosses the first interim analysis efficacy threshold and is considered safe (Figure 3-4), will be advanced to Part 3 seamlessly upon completion of enrollment of the Part 2 subjects in that arm (approximately 25 subjects).

The threshold has been chosen based on the probability that an observed response rate (RR) of the primary efficacy endpoint will be of clinical interest (i.e. 5 or more responders out of 10 subjects) for subjects with myelofibrosis.

The second interim analysis will be conducted after at least 25 subjects of each combination treatment arm in Part 2 have completed 8 cycles (arms with NIS793) or 6 cycles (all other arms) of treatment. A futility threshold will be applied to the combination treatments in the second interim analysis. The threshold has been chosen based on the probability that an observed RR of the primary efficacy endpoint will be of clinical interest (i.e. 5 or more responders out of 25 subjects) for subjects with myelofibrosis. Arms that fulfill the futility criteria shown in Figure 3-4 are declared futile and will not be eligible for Part 3. For arms that are not considered futile, i.e. arms that show preliminary efficacy, all available efficacy, safety, PK [redacted] data will be assessed and combination arms that do not have a manageable safety profile or have an unpredictable PK/PD profile will not be considered for Part 3. The second interim analysis is not required if a combination treatment is advanced in Part 3 based on the first interim analysis. Further details are provided in Section 12.

Figure 3-4 Pre-specified criteria for decision making in Part 2 for expansion into Part 3



^An arm is considered effective if there is a >80% probability that the true response rate (RR) for the primary endpoint is greater than 0.3, given the observed data (D). For an arm with n=10 subjects (1st interim analysis), an arm is considered effective if 5 or more subjects are responders.
*An arm is dropped for futility if there is a >50% probability that the true response rate (RR) for the primary endpoint is less than or equal to 0.2, given the observed data (D). For an arm with n=25 subjects (2nd interim analysis), an arm is considered futile if 4 or fewer subjects are responders.

Part 3: Expansion (Not applicable)

As the enrollment was permanently halted, the Part 3 will not be initiated, therefore the description below for Part 3 is not applicable.

The primary objective for Part 3 is to further characterize the efficacy of the combination treatment arms carried forward from Part 2. Only combination treatment arms that show preliminary efficacy, have a manageable safety profile, and a predictable PK/PD profile will be considered for expansion. A maximum of 5 combination treatments can be expanded in Part 3.

The efficacy of ruxolitinib combination treatment(s) chosen for expansion will be compared to ruxolitinib monotherapy. In addition to the ruxolitinib monotherapy arm and the combination treatment arm(s), Part 3 will contain an arm in which subjects receive 3 or 4 cycles of combination treatment followed by combination partner only i.e. stopping ruxolitinib ("ruxolitinib cessation arm"). The Part 3 subjects will be treated for at least 16 cycles (arms with NIS793) or 12 cycles (all other arms). In the ruxolitinib cessation arm, during cycle 4 for the ruxolitinib+NIS793 combination treatment and cycle 3 for all other combination treatments (depending on which combination treatment is chosen), ruxolitinib will be gradually tapered off at the investigator's discretion to 0 mg dose. Tapering ruxolitinib treatment should be done within at least 14 days. At Cycle 5 Day 1 (C5D1; for NIS793) or C4D1 (for other treatments) in the ruxolitinib cessation arm, the dose of ruxolitinib must be reduced to 0 mg. Following interruption of ruxolitinib, symptoms of myelofibrosis may return over a period of approximately one week. In case of any withdrawal symptoms reported, investigators may decide to re-start ruxolitinib treatment immediately based on the clinical judgement and the safety assessment of the subject.

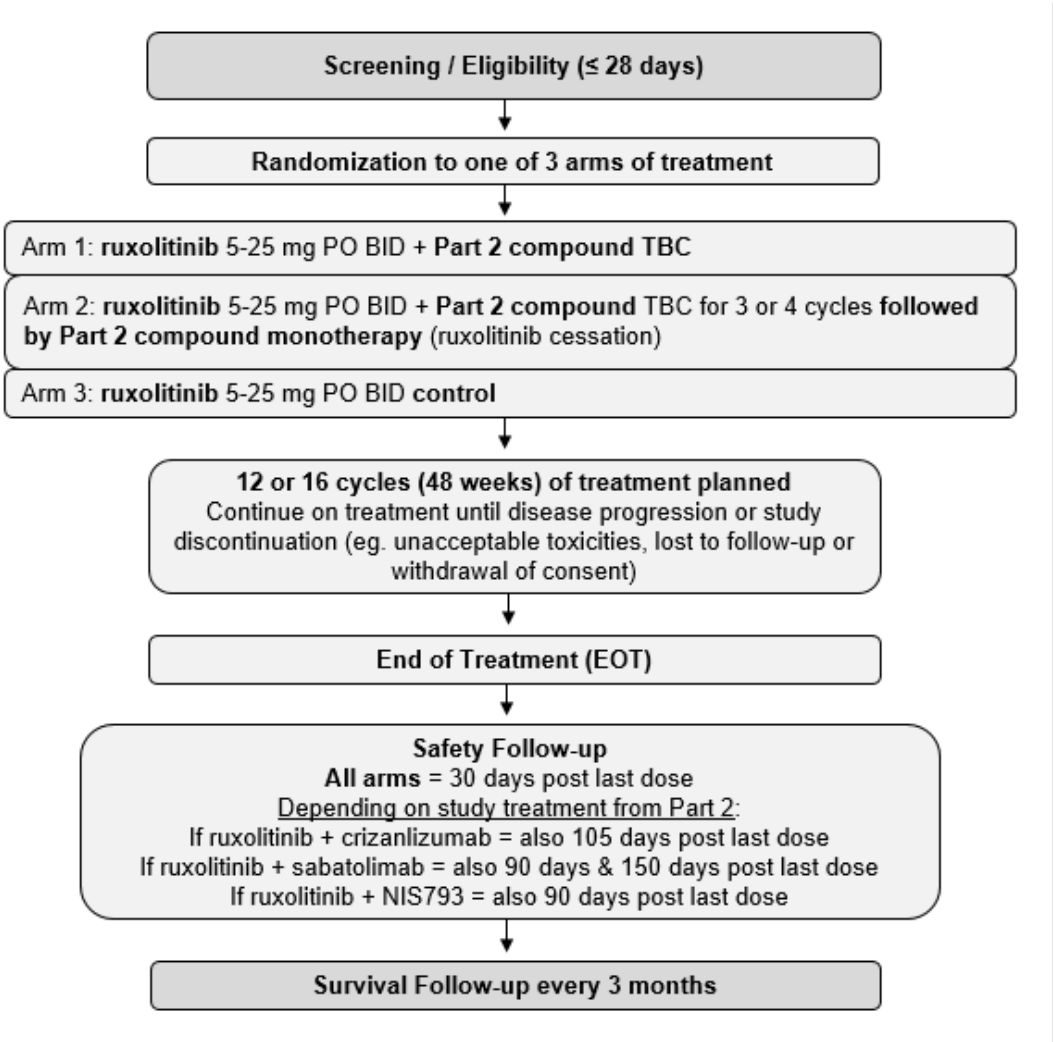
The ruxolitinib cessation arm is included to observe the effect of monotherapy of the combination partner. By comparing the primary endpoint RR of the combination treatment arm with the RRs in the ruxolitinib cessation arm and the ruxolitinib monotherapy arm, the contribution of each combination partner to the efficacy of the combination treatment can be assessed. Four cycles (arms with NIS793) or three cycles (all other arms) of combined treatment is deemed necessary to establish the effect of combined treatment on disease activity, based on experience with single agent ruxolitinib (COMFORT-I and COMFORT-II).

For each combination treatment chosen to be expanded in Part 3, subjects will be randomized to the chosen combination treatment arm, or a compound monotherapy arm (ruxolitinib cessation arm) or a ruxolitinib monotherapy arm, with a planned enrollment of approximately 20 subjects for the combination treatment arm, 10 subjects for the ruxolitinib cessation arm, and approximately 5 subjects for the ruxolitinib monotherapy control arm. There will be maximum number of 50 subjects in total for the common ruxolitinib monotherapy control arm in Part 2 and Part 3.

- Arm 1: Ruxolitinib 5-25 mg PO BID and novel compound from Part 2 (TBC)
- Arm 2: Ruxolitinib 5-25 mg PO BID and novel compound from Part 2 (TBC) for 3 or 4 cycles of treatment (depending on the combination treatment), followed by ruxolitinib cessation treatment (i.e. novel agent monotherapy control)
- Arm 3: Ruxolitinib 5-25 mg PO BID monotherapy control

An overview of the study design at the subject level in Part 3 is shown in Figure 3-5. A hypothetical example illustrating the randomization parts of the overall study design is shown in Section 16.8 (Appendix 8).

Figure 3-5 Overview of study design at subject level in Part 3 (Not applicable)



TBC: To be confirmed

4 Rationale

4.1 Rationale for study design

This is a phase Ib/II open-label, multi-center platform study in MF patients on ruxolitinib treatment for at least 12 weeks prior to first dose of study treatment, evaluating the safety, tolerability and preliminary efficacy of each novel ruxolitinib combination treatment. Using ruxolitinib as the backbone, this study will evaluate the combined effect of novel compounds that impact the hematopoietic environment through different mechanisms, which may deliver

transformational clinical benefits such as superior disease control or even reduction of the malignant clone.

Considering the number of potential targets and available compounds, an open platform design is applied for this study. In general, platform designs allow for simultaneous assessment of multiple treatments within a single disease under one master protocol (Ventz et al 2017, Saville and Berry 2016). An open platform design starts with a pre-defined fixed number of treatment arms but as new suitable treatments become available during the course of the trial, new treatment arms can be added. Those new arms are added based on evolving scientific rationale (e.g. mechanism of action), preclinical data and if an acceptable safety profile has been established. Furthermore, platform designs offer adaptive features such as dropping treatment arms for futility and declaring one or more treatments efficacious. The protocol will be amended if a new arm is added to the study in Part 1.

The platform study design methodology has been successfully applied as an accelerated mechanism to evaluate multiple compounds in various diseases, and has been implemented in recent clinical studies (e.g. I-SPY2, STAMPEDE, AML15, AML16) (Renfro and Mandrekar 2018, Ventz et al 2017, Woodcock and LaVange 2017, Saville and Berry 2016, Berry et al 2015).

The first 3 novel compounds chosen for inclusion in this study are siremadlin, crizanlizumab, and sabatolimab. Rineterkib and NIS793 were added in Amendment 4 of the protocol. At the time of the amendment, none of these compounds have been tested in MF patients previously, however a trial to investigate sabatolimab and NIS793 in MF patients who have had a sub-optimal response to a JAK inhibitor (including ruxolitinib) is planned (NCT04283526; CMBG453D1201). The specific rationale for the combinations selected is provided in Section 4.3.

The study was planned in three parts. In the context of the permanent enrollment halt, the study design has been revised revised as follows:

- Part 1: Dose escalation and safety run-in (recommended Phase II dose confirmation) including a core treatment phase and an extension treatment phase
- Part 2: Selection (unchanged as the only randomized subject has discontinued prior to amended protocol version 08)
- Part 3: Expansion (not applicable as it will never be initiated)

Part 1 of the study focuses on safety and tolerability, while Parts 2 and 3 assess the (preliminary) efficacy of siremadlin, crizanlizumab sabatolimab, rineterkib and NIS793 in combination with ruxolitinib, respectively.

Part 1 includes five separate arms (core treatment phase): two dose escalation arms to determine the RP2D for ruxolitinib in combination with siremadlin or rineterkib, and three safety run-in arms to confirm the selected doses of ruxolitinib in combination with crizanlizumab, sabatolimab or NIS793. The end of the core treatment phase will occur when amended protocol version 08 is implemented and after subjects have completed a minimum of 24 weeks of treatment.

As the enrollment was permanently halted, an extension treatment phase is added to the Part 1 design as a mechanism to provide access of ruxolitinib in combination for eligible and

benefitting subjects from Part 1 until the subjects complete 21 cycles in the extension treatment phase or until treatment discontinuation criteria is met, whichever occurs first (see Section 9.1).

This study will utilize a Bayesian Logistic Regression Model (BLRM) to identify the maximum tolerated dose (MTD) and/or RP2D for siremadlin in combination with ruxolitinib, and rineterkib in combination with ruxolitinib. The use of BLRMs is a well-established method to identify the MTD and/or RP2D. The adaptive BLRM will be guided by the escalation with overdose control (EWOC) principle to control the risk of DLT in future subjects on the study. The use of Bayesian response adaptive models for small datasets is widely accepted and endorsed by numerous publications (Neuenschwander et al 2008, Babb et al 1998) with its development and appropriate use one aspect of the Food and Drug Administration's (FDA) Critical Path Initiative. The decisions on new dose levels are made by the Investigators and Novartis study personnel in a dose escalation meeting based upon the review of patient tolerability and safety information (including the BLRM summaries of DLT risk) along with PK, PD and preliminary activity information available at the time of the decision.

While Part 1 of the study focuses on safety and tolerability, Parts 2 and 3 assess the preliminary efficacy of siremadlin, crizanlizumab, sabatolimab, rineterkib, and NIS793 in combination with ruxolitinib, respectively.

As the enrollment was permanently halted, the only randomized patient in Part 2 has discontinued prior to this amendment 08, and Part 3 will not be initiated, therefore the description for Parts 2 and 3 are not applicable.

Part 2 of the study includes combination arms and a ruxolitinib single agent arm. The single agent arm is included as no prior information for ruxolitinib in a clinical trial setting is available in the population considered in this study, i.e. subjects with a prior treatment of ruxolitinib for at least 12 weeks and a stable dose for at least four weeks prior to study entry. The size of Part 2 with a planned randomization of approximately 25 subjects per treatment combination arm is sufficient to identify treatments that show an activity that warrants further development.

Two interim analyses are planned for each treatment combination arm in Part 2. The first interim analysis is planned when at least 10 subjects in each combination treatment arm have completed Cycle 8 (treatment arms with NIS793) or Cycle 6 (all other treatment arms), or discontinued earlier. The second interim analysis is planned when at least 25 subjects in each combination treatment arm have completed Cycle 8 (treatment arms with NIS793) or Cycle 6 (all other treatment arms), or discontinued earlier. If a combination treatment is advanced in Part 3 based on the first interim analysis, the second interim analysis is not required. All available efficacy, safety, PK [redacted] data will be assessed to determine if a particular ruxolitinib combination treatment will be dropped due to futility based on pre-specified criteria (see Section 3) or if it demonstrates preliminary efficacy and should be considered for expansion in Part 3.

Part 3 is the expansion part of the study in the event that a combination treatment is deemed to be of interest for further development. New subjects will be randomized into this part of the study. The expansion part allows collection of additional data for the combination treatment and ruxolitinib single agent control, such that the combination treatment and ruxolitinib single agent can be compared. Part 3 will also include a combination partner single agent arm, where after an initial three months of combination therapy, ruxolitinib will be stopped to assess the

efficacy of the combination partner alone. This arm is called the ruxolitinib cessation arm. The expansion part of the study increases confidence in the ruxolitinib combination treatment selected after Part 2, prior to the start of a potential phase III trial.

This study design will allow for assessment of safety, tolerability, and preliminary efficacy of siremadlin, crizanlizumab, sabatolimab, rineterkib, and NIS793 in combination with ruxolitinib, respectively, while reducing subjects exposure to futile treatments.

Crossover or re-randomization of subjects to other combination arms, including better performing arms within a part of the study is not allowed. However, subjects are allowed to participate in another part of the study provided that all inclusion and none of the exclusion criteria are met and that they are not randomized twice. This means that Part 1 subjects could join Part 2 or Part 3 of the study and Part 2 and Part 3 subjects could participate in Part 1 of the study only. However, Part 2 subjects are not allowed to join Part 3 and vice versa.".

[redacted]

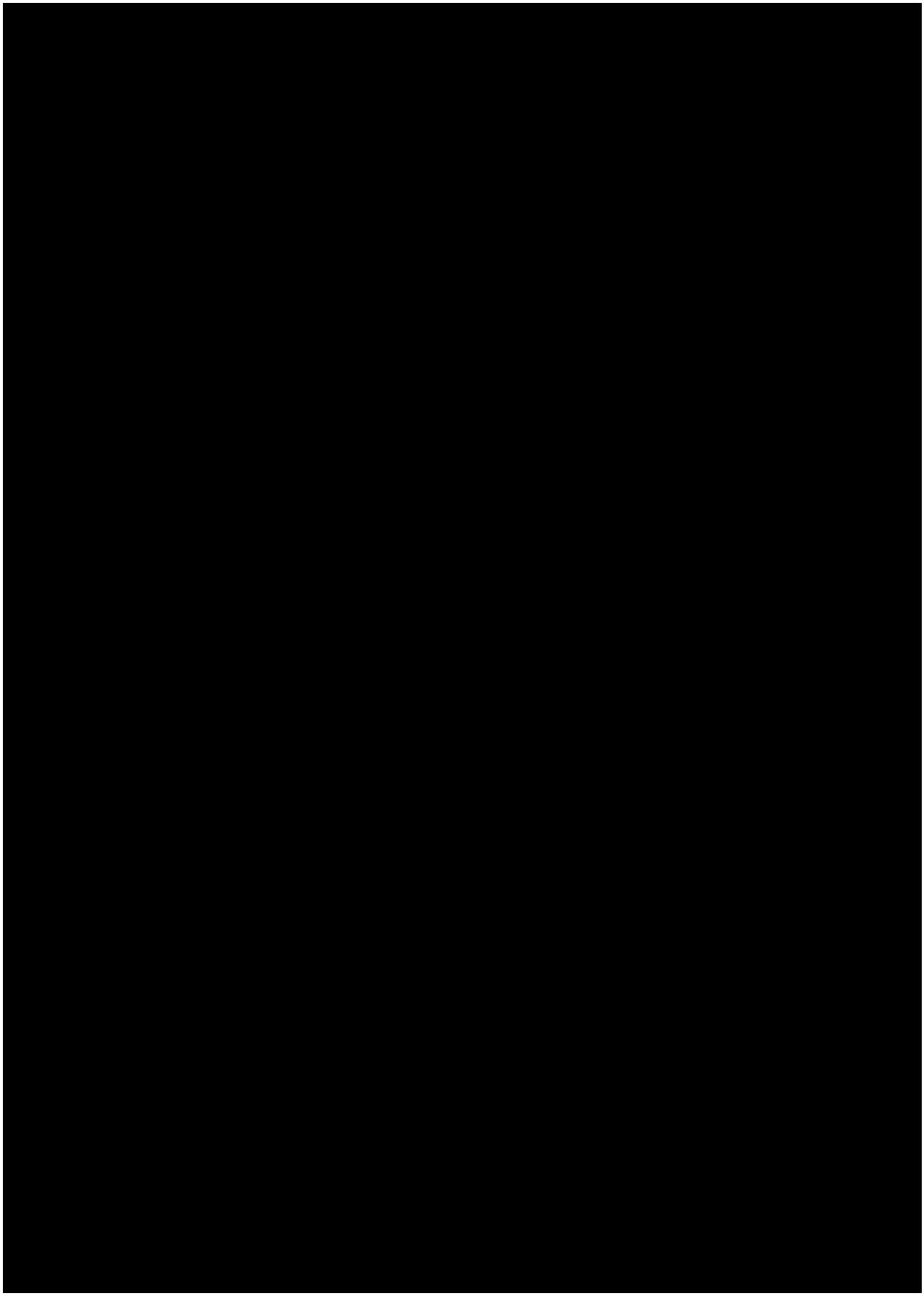
[redacted]

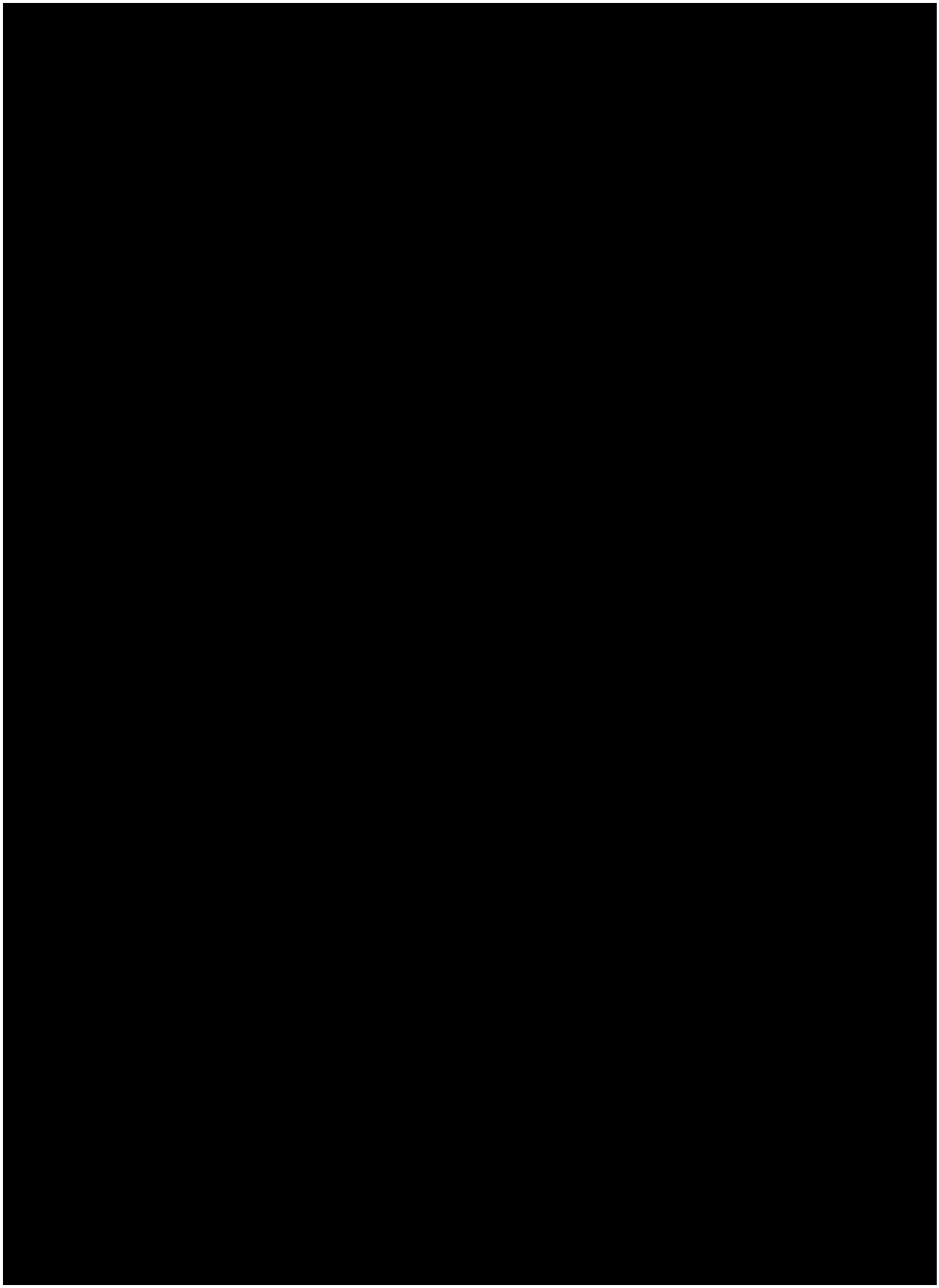
[redacted]

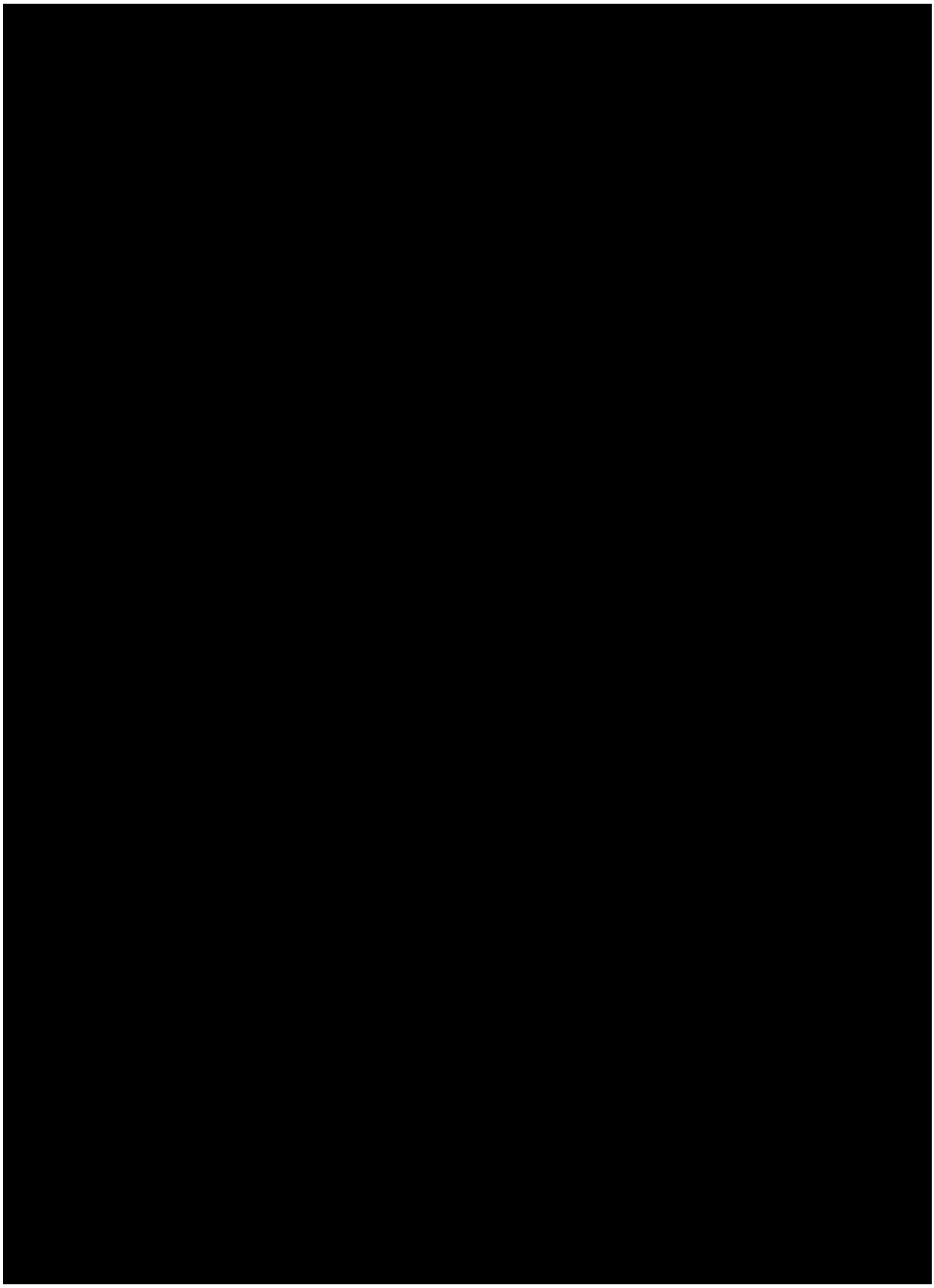
[redacted]

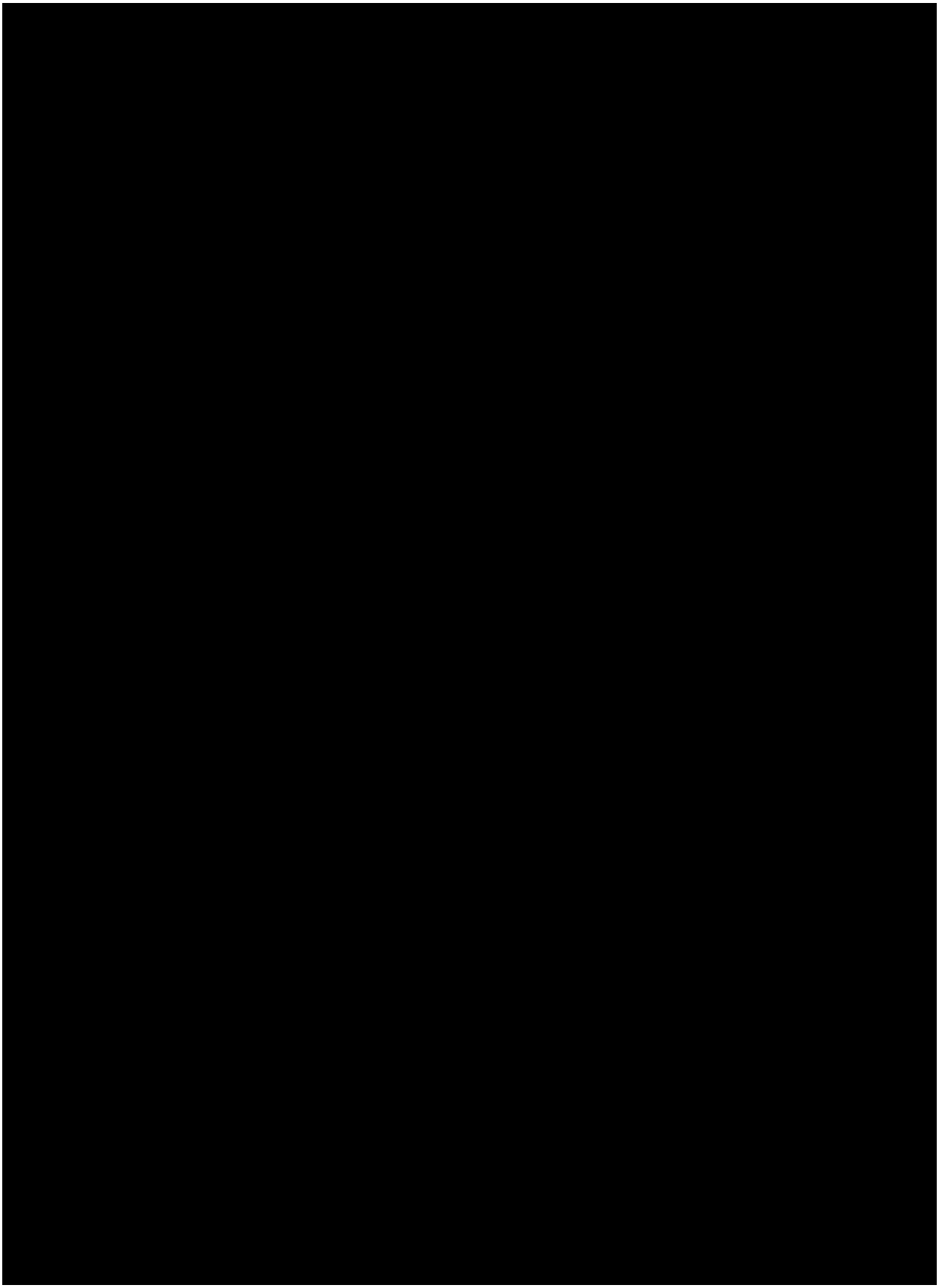
4.2.6 Extension Treatment Phase

Subjects eligible for the extension treatment phase will be assessed at the end of the core treatment phase by investigators (after the amended protocol version 08 is implemented), to ensure the regimen and dose subjects have been receiving is safe, tolerable and provides clinical benefit prior to continuation of the study treatment in the extension treatment phase.









4.4 Purpose and timing of interim analyses/design adaptations (Not applicable)

As the enrollment was permanently halted, the only randomized subject in Part 2 has discontinued prior to this amendment, and Part 3 will not be initiated therefore the description below for Parts 2 and 3 are not applicable as there will be no interim analyses for Parts 2 and 3.

Two interim analyses are planned for each combination treatment in Part 2. The first interim analysis will be conducted when at least 10 subjects of each combination treatment arm in Part 2 have completed 8 cycles (for all arms containing NIS793) or 6 cycles (all other arms) of treatment or discontinued from the study prior to completing Cycle 8 or Cycle 6, respectively. This is to determine whether combination treatment arms will be expanded in Part 3 seamlessly after the enrollment of the 25 subjects of the arm in Part 2 is completed, or whether the enrollment into Part 3 will only start once the second interim analysis is completed at the end of Part 2 (i.e. once all 25 subjects have completed 8 cycles (for all arms containing NIS793) or 6 cycles (all other arms) of treatment or discontinued from the study prior to completing Cycle 8 or Cycle 6, respectively). A threshold for outstanding preliminary efficacy will be applied to the combination treatments in the first interim analysis. An arm that crosses the threshold and is considered safe (see Figure 3-4), will continue to enroll into Part 3 seamlessly after enrollment of the Part 2 subjects in that arm is completed (approximately 25 subjects). The threshold has

been chosen based on the probability that an observed RR of the primary efficacy endpoint will be of clinical interest (i.e., 5 or more responders out of 10 subjects) for subjects with myelofibrosis.

The second interim analysis is planned after at least 25 subjects of each combination treatment arm in Part 2 have completed 8 cycles of treatment (for all arms containing NIS793) or 6 cycles of treatment (all other arms), or discontinued from the study prior to completing Cycle 8 or Cycle 6, to determine whether combination treatment arms will be dropped for futility or be considered for expansion in Part 3 based on pre-specified criteria shown in Figure 3-4. See Section 3 and Section 12.1 for further details.

4.5 Risks and benefits

Subjects enrolled in this study with a confirmed diagnosis of MF have experienced reduction in splenomegaly and improved QoL from clinical symptoms improvement as a result of ruxolitinib treatment. However, some of those subjects will present with sub-optimal treatment response through potential loss of the therapeutic effect of ruxolitinib in controlling clinical symptoms of MF or spleen size reduction. Other subjects may lose their response to ruxolitinib over time as inhibition of JAK-STAT signaling alone is not a curative strategy for MF. In addition, enrolled subjects also may experience cytopenia which cannot be controlled by ruxolitinib monotherapy. As such, there are limited treatment options for this population, which represents an unmet medical need in this disease setting. Therefore, the combinations of ruxolitinib with agents targeting other signaling pathways dysregulated in MF, tested in this study, may improve or reverse myelosuppression and provide disease-modifying effect.

Potential risks for each combination treatment are discussed in Section 4.2. The risk to subjects in this trial is minimized by compliance with the eligibility criteria and adherence to the study procedures, as well as, close clinical monitoring and implementation of the protocol defined dose-modifications guidelines and treatment discontinuation criteria and appropriate adverse event management.

Occurrence of an immune-related event is an anticipated risk in subjects treated with immunomodulatory therapies, such as NIS793 and sabatolimab. In the case of an immune-related event, there are dose modification and management guidelines, including for follow-up of toxicities, proposed by the protocol in relation consensus guidelines, such as those from the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) (Brahmer et al 2018; Haanen et al 2017; see Section 6.5.4 and Section 6.5.5).

Administration of monoclonal antibodies (mAbs) can be associated with infusion-related reactions (IRRs). Management and dose modification guidelines for IRRs are provided in Section 6.5.4 for crizanlizumab, sabatolimab, and NIS793.

A focused search for potentially severe IRRs (i.e. indicative of hypersensitivity/anaphylaxis or cytokine-release syndrome) identified 2 (1.8%) patients treated with crizanlizumab at 5 mg/kg in the pooled data set in SCD; the reported term was infusion-related reaction, none of which was serious. However, severe IRRs including cases requiring hospitalization have been described in ongoing clinical trials and the post-marketing setting. Additionally, a broad search for IRRs using an extensive list of potential signs and symptoms related to infusion reactions in

SCD patients treated with crizanlizumab, and occurring within 24 hours of the infusion, identified 28.8% of patients in the safety pool with at least one event. Most of these events were reported in 1 or 2 patients only, except for nausea (9.0%), headache (8.1%), arthralgia and back pain (4.5%), and fatigue and myalgia (2.7%). In the SUSTAIN study [clinicaltrials.gov number NCT01895361], IRRs using this broader search were more frequent in the 5 mg/kg arm (34.8%) compared to the placebo arm (21.0%). However, except for nausea, none of the events were reported with an absolute differences of more than 5% in the crizanlizumab 5 mg/kg vs. the placebo arm.

In summary, current data suggest that administration of crizanlizumab can be commonly associated with infusion related reactions, including pain events in patients with SCD, some of which can be severe and/or require hospitalization. Subjects should be monitored for potential signs and symptoms of IRRs, and participants instructed to contact the investigator/site when experiencing such events. In case of severe IRRs (eg. hypersensitivity/anaphylactic reaction), study treatment should be discontinued. For Japan only, subjects enrolled in the crizanlizumab arm of Part 1 (Arm 2) are required to be hospitalized in the first 7 days of study treatment.

Grade 4 tumor lysis syndrome (TLS) was observed in one subject administered siremadlin in study CHDM201X2101. During this study, subjects receiving siremadlin will be closely monitored for signs and symptoms of TLS before initiation and during a treatment cycle as per guidance in Section 6.6.

Cardiac events (AV block, atrial fibrillation, QT prolongation) associated with siremadlin treatment were observed in phase I and II monotherapy and combination trials. In this study, considering the potential cardiac risk of siremadlin, subjects treated with ruxolitinib and siremadlin combination will be monitored frequently in this study. See Section 8.4.2.

No cardiac events have been observed so far in studies with rineterkib (Janku et al 2020), however considering the potential cardiac risk for MEK inhibitors, subjects treated with ruxolitinib and rineterkib will be frequently monitored for cardiac events as outlined in Section 8.4.2. In addition, since left ventricular ejection fraction (LVEF) decrease is a class effect of MEK inhibitors, close monitoring with a multigated acquisition (MUGA) scan or echocardiogram (ECHO) is recommended. See Section 8.4.3.

Ocular events have been observed with MAPK pathway inhibitors such as MEK inhibitors, and in studies with rineterkib (Janku et al 2020). Therefore, in this study, subjects treated with ruxolitinib and rineterkib will undergo thorough ophthalmological assessments and be carefully monitored throughout the study, as outlined in Section 8.4.4.

For NIS793, based on currently available data, tubulointerstitial nephritis, vascular inflammation, endothelial hyperplasia, and cardiac valvulopathy have been observed in NIS793 animal studies but not in ongoing clinical studies. Cardiac and renal functions will be regularly monitored to minimize these risks.

No substantial additional risk for subject safety due to the SARS-CoV-2 virus and the COVID-19 pandemic has been identified at this time and therefore the benefit risk remains unchanged. In case of active COVID-19 infection, a careful benefit risk evaluation should be performed to determine whether a subject can remain on study treatment.

As in any clinical study, there may be unforeseen risks with ruxolitinib treatment alone or in combination with siremadlin, crizanlizumab, sabatolimab, rineterkib and NIS793, which could be serious.

Recommended guidelines for prophylactic or supportive management of study-drug induced adverse events are provided in Section 6.1.4 and in the most recent version of the Investigator's Brochure.

Women of child-bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and must agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

Periodic review of safety data will be performed by an independent DMC.

The enrollment halt decision was neither triggered by any safety signals nor safety concerns related to subjects receiving the study treatment, but due to the rapidly evolving competitive landscape in drug development for myelofibrosis, with multiple ongoing trials and continued challenges with recruitment.

4.6 Rationale for Public Health emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Population

As the enrollment was permanently halted, the only randomized patient in Part 2 has discontinued prior to this amendment, and Part 3 will not be initiated therefore the description below for Parts 2 and 3 are not applicable as there will be no further subjects enrolled in Parts 2 and 3.

The patient population will include male or female adults (age 18 or over) with a confirmed diagnosis of PMF as defined by the World Health Organization 2016 criteria (Arber et al 2016) or PPV-MF, or PET-MF according to International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) 2007 (Barosi et al 2008) criteria and in addition at baseline:

- Have Hb < 11g/dL (≤ 6.8 mmol/L), and
- Are on ruxolitinib therapy for at least 12 weeks with an unchanged ruxolitinib dose (range 5-25 mg BID) for the previous ≥ 4 weeks prior to first dose of study treatment, and
- Exhibit measurable splenomegaly demonstrated by spleen volume of ≥ 450 cm^3 by MRI or CT scan assessment or by palpable spleen measuring of ≥ 5 cm below left costal margin (LCM). MRI/CT scan up to 8 weeks prior to first dose of study treatment can be accepted.

The total number of subjects expected to enroll into the entire study, allowing for dropouts and non-evaluable patients, is approximately 240 assuming that 5 combination treatments from Part

1 are selected for Part 2, and that 1 of the 5 combination treatments is expanded in Part 3. The actual number of patients recruited will depend upon the number of dose levels tested in the dose escalation Part 1 and the number of combination arms carried into Parts 2 and 3. If all 5 combination treatments enter Part 3, then there will be a maximum of approximately 380 subjects in total in all 3 parts of the study

The investigator or designee must ensure that only patients who meet all of the following inclusion and none of the exclusion criteria at screening are assigned treatment in the study.

5.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Male or female subjects are at least 18 years of age at the time of signing the informed consent form (ICF). **For Japan only**: written consent is necessary both from the subject and his/her legal representative if he/she is under the age of 20 years.
2. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1 or 2.
3. Subjects have diagnosis of primary myelofibrosis (PMF) according to the 2016 World Health Organization (WHO) criteria, or diagnosis of post-ET (PET-MF) or post-PV myelofibrosis (PPV-MF) according to the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) 2007 criteria.
4. Palpable spleen of at least 5 cm from the left costal margin (LCM) to the point of greatest splenic protrusion or enlarged spleen volume of at least 450 cm^3 per MRI or CT scan at baseline (a MRI/CT scan up to 8 weeks prior to first dose of study treatment can be accepted).
5. Have been treated with ruxolitinib for at least 12 weeks prior to first dose of study treatment.
6. Are stable (no dose adjustments) on the prescribed ruxolitinib dose (between 5 and 25 mg BID) for ≥ 4 weeks prior to first dose of study treatment.
7. Hemoglobin < 11 g/dL (≤ 6.8 mmol/L).
8. Absolute neutrophil count (ANC) ≥ 1000/μL.
9. Part 1: Platelet counts ≥ 75,000/μL
10. Part 2 and Part 3: Platelet counts ≥ 50,000/μL.
11. Subjects must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.

5.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study.

1. Not able to understand and to comply with study instructions and requirements.
2. Received any investigational agent for the treatment of MF (except ruxolitinib) within 30 days of first dose of study treatment or within 5 half-lives of the study treatment, whichever is greater.
3. Received any investigational cancer vaccine or immunotherapy within 6 months prior to first dose of study treatment.
4. Peripheral blood blasts count of > 10%.

5. Inadequate liver function defined by any of these: Total bilirubin ≥ 2.5 x ULN and subsequent determination of direct bilirubin ≥ 2.5 x upper limit of normal (ULN); Alanine aminotransferase (ALT) > 2.5 x ULN; Aspartate aminotransferase (AST) > 2.5 x ULN.
6. Severely impaired renal function defined by: Estimated creatinine clearance < 30mL/min.
7. Active bacterial (including active and latent tuberculosis), fungal, parasitic, or viral infection that requires therapy.
8. Known history of human immunodeficiency virus (HIV) infection or in the opinion of the investigator other clinically significant immunodeficiency syndromes such as X-linked agammaglobulinemia and common variable immune deficiency.
9. Evidence of active HBV or HCV viral infection (HBsAg in the absence of HBsAb OR HCV Ab positive with HCV RNA positive). Subjects whose disease is controlled under antiviral therapy should not be excluded.
10. History of progressive multifocal leuko-encephalopathy (PML).
11. History of a second primary malignancy in the past 3 years in need of systemic treatment.
12. History or current diagnosis of uncontrolled or significant cardiac disease including any of the following:
    - Acute Myocardial infarction, coronary stenting, or bypass surgery within the last 6 months
    - Uncontrolled congestive heart failure requiring treatment (New York Heart Association Grade ≥ 2), LVEF < 50% as determined by multigated acquisition (MUGA) scan or echocardiogram (ECHO), or uncontrolled hypertension defined by blood pressure ≥ 140 (systolic) /90 (diastolic) mmHg at rest (average of 3 consecutive readings) despite medical treatment
    - Unstable angina pectoris within the last 6 months
    - For NIS793 arms only in Part 1 and all arms in Part 2 and 3 if NIS793 is open for enrollment:
    - Cardiac valvulopathy ≥ Grade 2
    - Elevated cardiac enzymes (troponin I) elevation > 2x ULN
    - Medical history or current diagnosis of myocarditis
13. History or current diagnosis of ECG abnormalities indicating significant risk of cardiac disease such as:
    - Resting QTcF ≥ 470 msec at pretreatment (baseline) for both male and female or impossibility to determine QTc
    - Concomitant clinically significant cardiac arrhythmias (e.g. uncontrolled atrial flutter / fibrillation, ventricular tachycardia), and clinically significant second or third degree AV block without a pacemaker
    - History of familial long QT syndrome or know family history of Torsades de Pointe or any of the following:
    - Risk factors for Torsades de Pointe including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia
    - Inability to determine the QTcF interval

14. Any condition which, in the opinion of the investigator, is likely to interfere with the successful collection of the measurements required for the study
15. Contraindication or hypersensitivity to any drug or metabolites from similar class as study drug or to any excipients of the study drug formulation.
16. Any other known disease that could compromise participation in the study including gastrointestinal (GI) disorders impacting absorption of ruxolitinib or siremadlin (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection), evidence of major active bleeding or history of bleeding diathesis or major coagulopathy.
17. Had history of documented severe hypersensitivity reactions/immunogenicity to a prior biologic product in any treatment arm OR received a monoclonal antibody or immunoglobulin-based agent:
    - For treatment arms with NIS793, crizanlizumab or sabatolimab within 1 year of screening,
    - For treatment arms with rineterkib or siremadlin arms within <=4 weeks of screening or <=5 half-lives whichever is shorter for rineterkib or siremadlin arms.
    - For Part 2 and Part 3, the longest window will apply based on the compounds opened for randomization.
18. Significant immune deficiency (including chronic use of immunosuppressive drugs) in the opinion of the investigator.
19. Pregnant females or females who have given birth within the past 90 days or who are breastfeeding.
20. Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 30 days after the last dose of single-agent ruxolitinib (control/monotherapy), for 30 days after the last dose of siremadlin for subjects on ruxolitinib + siremadlin (or siremadlin monotherapy), for 30 days after the last dose of rineterkib for subjects on ruxolitinib + rineterkib (or rineterkib monotherapy), for 90 days after the last dose of NIS793 for subjects on ruxolitinib + NIS793 (or NIS793 monotherapy), 105 days after the last dose of crizanlizumab for subjects on ruxolitinib + crizanlizumab (or crizanlizumab monotherapy), and for 150 days after the last dose of sabatolimab for subjects on ruxolitinib + sabatolimab (or sabatolimab monotherapy).

    Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject

- Use of an intrauterine device (IUD) or intrauterine system (IUS). Any forms of hormonal contraception for example oral, injectable, implanted, transdermal hormonal patch or hormonal vaginal ring are excluded from use

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (eg, age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks prior to start of study treatment. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child bearing potential.

If local regulations deviate from the contraception methods listed above (for women of child-bearing potential or male) to prevent pregnancy, local regulations apply and will be described in the ICF.

21. Sexually active males unless they use a condom during intercourse while taking siremadlin or rineterkib and for 2 weeks after siremadlin or rineterkib discontinuation, and thus do not attempt to father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
22. History of drug-induced pneumonitis or current pneumonitis.
23. Use of erythropoietin stimulating agents (ESA) $\leq$ 4 weeks prior to first dose of study treatment.
24. Splenic irradiation within 6 months prior to the first dose of study drug.
25. Received blood platelet transfusion within 28 days prior to first dose of study treatment. Note: PRBC transfusions are permitted.
26. Subjects with known TP53 mutation or deletion of TP53.
27. Currently receiving treatment with drug or herbal medications that meet any of the following criteria:
    - Require the use of herbal preparations/medications and dietary supplements (except for vitamins) within 7 days prior to first dose of study treatment or are expected to use such products during the entire study.
    - Receiving fluconazole at doses higher than 200 mg daily.
    - Require treatment with moderate or strong CYP3A4/5 inducers within 14 days prior to first dose of study treatment, and cannot be discontinued or switched to alternative medication prior to first dose of study treatment.
    - Require treatment with strong CYP2C9 inducers within 14 days prior to first dose of study treatment, and cannot be discontinued or switched to alternative medication prior to first dose of study treatment.
    - Require treatment with moderate or strong CYP3A4/5 inhibitors within 48 hours prior to first dose of study treatment, and cannot be discontinued or switched to alternative medication prior to first dose of study treatment.
    - Require treatment with strong CYP2C9 inhibitors within 48 hours prior to first dose of study treatment, and cannot be discontinued or switched to alternative medication prior to first dose of study treatment.

- Require treatment with substrates of CYP3A4/5 with a narrow therapeutic index within 24 hours prior to first dose of study treatment.

(NOTE: the above criteria is consolidated across ALL treatment arms to accommodate for subject randomization process. For 'treatment arm' specific restrictions related to concomitant medication while on 'study treatment', please refer to Section 6.2.2)

28. Eligible for allogeneic hematopoietic stem cell transplantation (ASCT) at the time of enrollment.
29. Use of live vaccines within 30 days prior to first dose of study treatment.
30. Use of systemic steroid therapy and other immunosuppressive drugs within 14 days prior to first dose of study treatment (> 10 mg/day prednisone or equivalent). Topical, inhaled, nasal, ophthalmic steroids are allowed. Replacement therapy, steroids given in the context of a transfusion are allowed and not considered a form of systemic treatment.
31. Occurrence of any clinically significant bleeding events within 6 months prior to first dose of study treatment.
32. For patients treated with rineterkib in Part 1 and for all patients in Part 2 and Part 3 (if an rineterkib arm is included in the randomization for Part 2 or Part 3): Pre-existing retinal vein occlusion (RVO) or current risk factors (apart from the underlying MF) for RVO (e.g. uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes).

5.3 Eligibility for extension treatment phase

Subjects eligible for inclusion in the extension treatment phase must meet all the following criteria:Inclusion criteria

1. Signed informed consent for the extension treatment phase must be obtained ect who is ongoing in the core treatment phase.
2. Subject who demonstrates clinical benefit of treatment in core treatment phase per investigator's assessment.

Exclusion criteria

Subjects meeting any of the following criteria are not eligible for the extension treatment phase:

1. Subject meets any of study treatment discontinuation criteria outlined in Section 9.1
2. Subject currently has evidence of treatment failure as determined by the investigator, following treatment in core treatment phase.
3. Subject enrolled in another interventional study.
4. Subject has evidence of non-compliance to study procedures or withdrew consent in core treatment phase.
5. Subject currently has unresolved toxicities for which study treatment has been interrupted in the core treatment phase.
6. Subject has local access to alternative myelofibrosis treatment including those currently under investigation in clinical trials as assessed suitable in the opinion of the investigator.

6 Treatment

6.1 Study treatment

For this study, the term 'investigational drug' refers to ruxolitinib, siremadlin, crizanlizumab sabatolimab, rineterkib, or NIS793 labelled and supplied by Novartis as listed in Table 6-1. For USA only, ruxolitinib will be supplied locally as commercially available either by Novartis or by the site pharmacy. The term 'combination treatment' refers to ruxolitinib administered in combination with siremadlin (HDM201), crizanlizumab (SEG101), sabatolimab (MBG453), rineterkib (LTT462) or NIS793. The term 'study treatment' refers to any single agent treatment (investigational drug) or combination treatment that a subject has been allocated to in Part 1 or randomized to in Parts 2 and 3 of the study.

6.1.1 Investigational and control drugs

Table 6-1 Investigational drugs

Investigational Drug (Name and Strength)	**Pharmaceutical Dosage Form**	**Route of Administration**	**Supply Type**	**Sponsor (global or local)**
Ruxolitinib (INC424) 5 mg	Tablet	Oral use	open-label supply; bottles	Sponsor (global and local for USA only)
Ruxolitinib (INC424) 10 mg (not applicable*)	Tablet	Oral use	open-label supply; bottles	Sponsor (local, USA only)
Ruxolitinib (INC424) 15 mg (not applicable*)	Tablet	Oral use	open-label supply; bottles	Sponsor (local, USA only)
Ruxolitinib (INC424) 20 mg (not applicable*)	Tablet	Oral use	open-label supply; bottles	Sponsor (local, USA only)
Ruxolitinib (INC424) 25 mg (not applicable*)	Tablet	Oral use	open-label supply; bottles	Sponsor (local, USA only)
Siremadlin (HDM201) 10 mg	Capsule	Oral use	open-label subject packs; bottles	Sponsor (global)
Siremadlin (HDM201) 20 mg	Capsule	Oral use	open-label subject packs; bottles	Sponsor (global)
Siremadlin (HDM201) 40 mg (not applicable#)	Capsule	Oral use	open-label subject packs; bottles	Sponsor (global)
Crizanlizumab (SEG101) 100 mg / 10 mL (not applicable**)	Concentrate for solution for infusion	Intravenous use	open-label subject packs; vials	Sponsor (global)
Sabatolimab (MBG453) 100 mg / 1 mL (not applicable**)	Concentrate for solution for infusion	Intravenous use	open-label subject packs; vials	Sponsor (global)

Investigational Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Sabatolimab (MBG453) 400 mg / 4 mL (not applicable**)	Concentrate for solution for infusion	Intravenous use	open-label subject packs; vials	Sponsor (global)
Rineterkib (LTT462) 100 mg	Capsule	Oral use	open-label subject packs; bottles	Sponsor (global)
Rineterkib (LTT462) 50 mg (not applicable**)	Capsule	Oral use	open-label subject packs; bottles	Sponsor (global)
NIS793 700mg / 7mL (not applicable**)	Concentrate for solution infusion (Liquid in vial)	Intravenous use	open-label subject packs; vials	Sponsor (global)
From amended protocol version 08: * Investigational Drug provided locally by the sponsor in USA is not applicable as USA will not be initiated due to enrollment halt. ** Investigational Drugs which are not applicable as they will no longer be investigated due to enrollment halt, and there are no ongoing subjects receiving such drug. From amended protocol version 09: # Investigational Drug strengths which are not applicable as they will no longer be investigated due to enrollment halt, and there are no ongoing subjects receiving such drug strength.				

A dose of 30 mg siremadlin will also be used in the study as a combination of the 10 mg and 20 mg capsules.

The Part 1 extension treatment phase will use similar clinical supplies as the Part 1 core treatment phase.

6.1.2 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

Ancillary treatments for potential infusion reactions with crizanlizumab, sabatolimab and NIS793

[redacted] If a subject experiences an infusion reaction, he/she may receive pre-medication on subsequent dosing days. The pre-medication should be chosen per institutional standard of care,

at the discretion of the treating physician. If a subject experiences a Grade 3 or Grade 4 infusion reaction, the investigational drug should be discontinued.

Acute allergic reactions should be treated as needed per institutional standard of care. In the event of anaphylactic/anaphylactoid reactions, this includes any therapy necessary to restore normal cardiopulmonary status. [redacted]

6.1.3 Treatment arms/group

This is an open-label, three-part study. The dose of ruxolitinib used for all subjects in any part of the study (5-25 mg PO BID), whether taken as a single agent control or in combination with one of the 5 novel compounds, should not change from the stable dose used prior to first dose of study treatment. This applies also to the extension treatment phase.

Part 1: Dose escalation and safety run-in

In Part 1 of the study, subjects will be allocated to one of the following 5 treatment arms (core treatment phase):

- Arm 1: Ruxolitinib 5-25 mg PO BID and siremadlin at various dose levels (either 10 mg, 20 mg (starting dose), 30 mg or 40 mg) PO QD on Days 1 to 5 of a 28-day cycle
- Arm 2: Ruxolitinib 5-25 mg PO BID and crizanlizumab 5 mg/kg IV Q4W with a loading dose administered at C1D15
- Arm 3: Ruxolitinib 5-25 mg PO BID and sabatolimab 800 mg IV Q4W
- Arm 4: Ruxolitinib 5-25 mg PO BID and rineterkib at various dose levels (either 100 mg, 200 mg (starting dose) or 300 mg) PO QD in 28-day cycles
- Arm 5: Ruxolitinib 5-25 mg PO BID and NIS793 2100 mg IV Q3W

For Arm 1 and Arm 4, a dose escalation will be performed to determine the RP2D of the combination treatment of siremadlin with ruxolitinib and rineterkib with ruxolitinib, respectively. It is estimated that approximately 18 subjects will be included in the dose escalation part for the combination of ruxolitinib and siremadlin in Arm 1, approximately 6 subjects in each of 3 proposed cohorts. Approximately 12 subjects will be included in the dose escalation part for the combination or ruxolitinib and rineterkib in Arm 4. For Arm 2 (ruxolitinib + crizanlizumab), Arm 3 (ruxolitinib + sabatolimab) and Arm 5 (ruxolitinib + NIS793), a safety run-in based on approximately 6 subjects per treatment arm will be conducted.

From the time of implementation of the amended protocol version 08, subjects who have received the combination treatment for a minimum of 24 weeks in the core treatment phase of Part 1 and are benefitting from the allocated combination treatment may be eligible to continue the same combination treatment in the extension treatment phase.

As the enrollment was permanently halted, the only Part 2 subject who was randomized to Arm 6 has been prematurely discontinued, and Part 3 will not be initiated, therefore the descriptions below for Parts 2 and 3 are not applicable.

Part 2: Selection (not applicable)

In Part 2 of the study, subjects will be randomized to one of the following 6 treatment arms in groups with approximately 25 subjects per combination treatment arm and up to approximately 30 subjects per ruxolitinib monotherapy control arm (no (0) subjects will be allocated to each non-selected arm if a combination treatment does not enter Part 2):

- Arm 1: Ruxolitinib 5-25 mg PO BID and siremadlin at the RP2D from Part 1 PO QD on Days 1 to 5 of a 28-day cycle
- Arm 2: Ruxolitinib 5-25 mg PO BID and crizanlizumab 5 mg/kg IV Q4W
- Arm 3: Ruxolitinib 5-25 mg PO BID and sabatolimab 800 mg IV Q4W
- Arm 4: Ruxolitinib 5-25 mg PO BID and rineterkib at the RP2D from Part 1 PO QD in 28-day cycles
- Arm 5: Ruxolitinib 5-25 mg PO BID and NIS793 2100 mg IV Q3W
- Arm 6: Ruxolitinib 5-25 mg PO BID monotherapy control

Part 3: Expansion (not applicable)

In Part 3 of the study, subjects will be randomized to combination treatment arms or monotherapy arms with a planned enrollment of approximately 20 subjects for the combination treatment arms, 10 subjects for the cessation arms (novel agent monotherapy arm), and a common ruxolitinib monotherapy control arm. There will be maximum number of 50 subjects in total for the common ruxolitinib monotherapy control arm in Part 2 and Part 3:

- Arm 1: Ruxolitinib 5-25 mg PO BID and novel compound from Part 2 (TBC)
- Arm 2: Ruxolitinib 5-25 mg PO BID and novel compound from Part 2 (TBC) for 3 or 4 cycles of study treatment (depending on the combination treatment), followed by ruxolitinib cessation treatment (i.e. novel agent monotherapy control)
- Arm 3: Ruxolitinib 5-25 mg PO BID monotherapy control

6.1.4 Guidelines for continuation of treatment

For continuation of study treatment, please refer to Section 6.5.4 dose modifications and Section 6.5.5 follow-up for toxicities.

6.1.5 Treatment duration

The duration of core treatment phase in Part 1 (Dose escalation and safety run-in) is planned for 6 or 8 cycles depending on the treatment arm (24 weeks). For all arms containing NIS793,

which has a 21-day cycle (Q3W), the duration of treatment is 8 cycles. For all other arms, which have 28-day cycles the duration of treatment is 6 cycles.

As of amended protocol version 08 implementation, subjects who are in the core treatment phase of Part 1 and are benefitting from the allocated combination treatment may be eligible to continue the same combination treatment in the extension treatment phase. The duration of the extension treatment phase is planned for a maximum of 21 cycles and will continue until all subjects have reached the planned duration or have discontinued treatment earlier (see Section 9.1). As the enrollment was permanently halted, the only Part 2 patient who was randomized to Arm 6 has been prematurely discontinued, and Part 3 will not be initiated, therefore the descriptions below for Parts 2 and 3 are not applicable.

In Part 2 (Selection) and Part 3 (Expansion) the planned duration of treatment is 12 or 16 cycles depending on the study treatment arm (48 weeks), as noted above for Part 1.

The subject will start study treatment on Cycle 1 Day 1 (C1D1) and each cycle is either 21 days (all arms containing NIS793) or 28 days (all other arms).

Subjects may be discontinued from treatment earlier due to unacceptable toxicity, disease progression or treatment is discontinued at the discretion of the investigator or the subject.

Subjects who complete participation in this trial and continue to derive clinical benefit from the treatment based on the investigator's evaluation may receive post-trial access. Post Trial Access (PTA) means the provision of treatment to trial participants following their completion of trial participation. PTA will be provided until one of the following is met: participant no longer derives clinical benefit, investigator discontinues treatment, launch or reimbursement (where applicable), treatment fails to achieve registration in the trial participant's country, or the clinical program is discontinued for any other reason. Mechanisms for provision of PTA may include an extension phase to this study, a separate extension protocol, a rollover protocol, provision of the Novartis investigational product in a non-trial setting (known as post-study drug supply [PSDS]) when no further safety or efficacy data are required, or any other mechanism appropriate for the country.

Following the enrollment halt decision, the post-trial access solution for this study is the extension treatment phase introduced with amended protocol version 08.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

Prior ruxolitinib treatment of at least 12 weeks prior to the first dose of study treatment must be recorded in the eCRF, including the dosing information up to 4 weeks prior to study treatment. The subject must be told to notify the investigational site about any new medications he/she takes within 30 days prior to initial dosing until the completion of end of study (EOS) visit.

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) taken within 30 days prior to first dose of study treatment must be recorded on the appropriate case report forms (CRFs).

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before

enrolling a subject or allowing a new medication to be started. If the subject is already enrolled, contact Novartis to determine if the subject should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

The following medications have restrictions on their use during the study, including the extension treatment phase:

- In patients for whom low molecular weight heparin or any other anti-coagulant, and anti-platelet (including aspirin ≤ 150 mg/day) drug use will be initiated, the degree of thrombocytopenia should be considered, coagulation parameters monitored, and dose of anti-coagulant adjusted accordingly.
- Granulocyte growth factors (G-CSF) may be used for severe neutropenia at the Investigator's discretion while study medication is being withheld.
- The drug label for ruxolitinib should be consulted for guidance on concomitant therapies and in consideration of the below cautionary use under Section 6.2.1.1.1 and Section 6.2.1.1.2 for the respective combinations arms.
- Concomitant use of moderate CYP2C9 inducers are to be used with caution.
- Concomitant use of moderate CYP2C9 inhibitors are to be used with caution

6.2.1.1.1 Permitted concomitant therapy requiring caution and/or action: Specific to combination arm ruxolitinib + siremadlin

In addition to the permitted medications requiring cautionary use listed under Section 6.2.1.1, the following applies to treatment arm ruxolitinib + siremadlin:

- CYP3A4 sensitive substrates are to be used with caution 24 hours before, during and 48 hours after siremadlin administration
- OATP1B1 substrates are to be used with caution 24 hours before, during and 48 hours after siremadlin administration
- MATE1 substrates are to be used with caution 24 hours before, during and 48 hours after siremadlin administration
- P-gp inhibitors are to be used with caution on all days of siremadlin administration

Refer to Table 16-1 in Section 16.1 (Appendix 1) for a detailed list on concomitant medications to be used with caution.

6.2.1.1.2 Permitted concomitant therapy requiring caution and/or action: Specific to ruxolitinib single agent arm, or combination arm ruxolitinib + crizanlizumab, or ruxolitinib + sabatolimab, or ruxolitinib + NIS793

In addition to the permitted medications requiring cautionary use listed under Section 6.2.1.1, the following applies for treatment arms ruxolitinib + crizanlizumab, ruxolitinib + sabatolimab, ruxolitinib + NIS793, and ruxolitinib single agent, including during the extension treatment phase:

- Concomitant use of moderate CYP3A4 inducers is discouraged during the study, and investigators should seek alternatives where possible. No dose adjustments are needed when

moderate CYP3A4 inducers are co-administered with study treatment. However, any concomitant use of moderate CYP3A4 inducers must be documented (Section 16.1).

- Vaccination against COVID-19 is allowed, unless these are attenuated vaccines, but should not be administered on the same day of study treatment administration to avoid potential overlapping adverse events. (Note: Use of COVID-19 live vaccine is prohibited during the study (Section 6.2.2)).

Refer to Table 16-1 in Appendix 1 (Section 16.1) for a detailed list on concomitant medications to be used with caution.

6.2.1.1.3 Permitted concomitant therapy requiring caution and/or action: Specific to combination arm ruxolitinib + rineterkib

In addition to the permitted medications requiring cautionary use listed under Section 6.2.1.1, the following applies to treatment arm ruxolitinib + rineterkib, including during the extension treatment phase:

- Substrates of CYP3A4 with narrow therapeutic index
- Sensitive substrates of CYP3A
- Moderate CYP3A inhibitors or inducers.
- Moderate CYP2C8 inhibitors or inducers.
- Proton pump inhibitors and agents that modify gastric pH. If antacids and/or H2 receptor antagonists are indicated, follow the guideline provided in Appendix 1 regarding timing of administration of these agents relative to rineterkib dosing.
- Drugs with known risk of Torsades de Pointes.

6.2.2 Prohibited medication

The following medications, herbal remedies or foods are prohibited during the study, including during the extension treatment phase:

- Any investigational medication (other than ruxolitinib, siremadlin, crizanlizumab, sabatolimab, rineterkib, or NIS793) that is not approved for any indication. Use of such medications within 30 days, prior to the first dose of study treatment, or within 5 half-lives of the study treatment, whichever is greater, and during the study through the Safety Follow-up Visit is prohibited.
- Aspirin > 150 mg/day
- Any use of ESAs.
- Any other medication for the treatment of myelofibrosis, including but not limited to:
  - Hydroxyurea (Hydrea, Hydroxycarbamide)
  - Busulfan
  - Interferon
  - Lenalidomide
  - Thalidomide
  - Anagrelide
  - Fedratinib

- Use of systemic steroid therapy and other immunosuppressive drugs is prohibited within 14 days prior to starting study treatment (> 10 mg/day prednisone or equivalent) and during the study treatment period except for the treatment of infusion reaction, treatment of immune-related AEs (irAEs), for prophylaxis against imaging contrast dye allergy, replacement-dose steroids in the setting of adrenal insufficiency (provided this is ≤ 10 mg/day prednisone or equivalent) or treatment of transient exacerbation of other underlying diseases such as chronic obstructive pulmonary disease requiring treatment for ≤ 3 weeks.
- Systemic corticosteroids required for control of infusion reactions or irAEs must be tapered and be at non-immunosuppressive doses (≤ 10 mg/day prednisone or equivalent) before the next study treatment administration. If more than 10 mg/day prednisone is used, study treatment should be interrupted until the subject receives 10 mg/day or less of prednisone.
- Topical, inhaled, nasal, ophthalmic steroids are allowed.
- Replacement therapy, steroids given in the context of a transfusion are allowed and not considered a form of systemic treatment.
- Use of live vaccines within 30 days prior to starting treatment and at any time during treatment period. Refer to Section 6.2.2.2 for the restriction of vaccines for the respective combination arms during study treatment.
- Use of strong CYP3A4/5 inhibitors are prohibited within 48 hours prior to starting treatment. When such a concomitant administration of a strong CYP3A4 inhibitor (see Table 16-2 in Appendix 2 (Section 16.2) for a listing of these medications) is required for patient management, the dose of ruxolitinib must be adjusted as described in Section 6.2.2.4 in accordance with the respective treatment arm. **Note for Part 1, use of strong CYP3A4/5 inhibitors are strictly prohibited up to end of Cycle 2, as a dose adjustment for ruxolitinib is not permitted within this period**.
- Herbal preparations/medications and dietary supplements (except for vitamins) are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Subjects should stop using these herbal medications 7 days prior to first dose of study drug.
- Subjects should be instructed to avoid consumption of grapefruit, grapefruit hybrids, pummelos, star-fruit, Seville oranges or products containing the juice of each during the entire study, due to potential CYP3A4 interaction with the study medications.
- Fluconazole doses greater than 200 mg daily are prohibited in all combination arms. In addition, all doses of fluconazole are prohibited in combination arm ruxolitinib + siremadlin (see Section 6.2.2.1). The drug label for ruxolitinib should be consulted for guidance on concomitant therapies, however, it must be in consideration of the restrictions under Section 6.2.2, Section 6.2.1.1 and Section 6.2.2.2 for the respective combinations arms.
- Use of strong inducers of CYP3A4/5 are prohibited within 14 days prior to starting and at any time during the study treatment period as ruxolitinib, siremadlin and rineterkib are CYP3A4 substrate.

- Use of strong inducers of CYP2C9 are prohibited within 14 days prior to starting treatment and at any time during the study treatment period as CYP2C9 is a major contributor to ruxolitinib metabolism.
- Use of strong inhibitors of CYP2C9 are prohibited within 48 hours prior to starting treatment and at any time during the study treatment period.

6.2.2.1 Prohibited medication specific to combination arm ruxolitinib + siremadlin

In addition to the prohibited medications listed under Section 6.2.2, the following medications are prohibited during the study, including the extension treatment phase, or prohibited within a defined time window:

- Use of moderate inducers of CYP3A4/5 are prohibited within 14 days prior to starting and at any time during the study treatment period as both ruxolitinib and siremadlin are primarily metabolized by CYP3A4
- Moderate or strong inhibitors of CYP3A4/5 are prohibited during 48 hours before and 48 hours after siremadlin administration
- Use of CYP3A4/5 substrates with a narrow therapeutic index (NTI) are prohibited 24 hours before and 48 hours after siremadlin administration as in vitro experiments have shown siremadlin to be both a time-dependent and reversible inhibitor of CYP3A4/5

Refer to Table 16-2 in Appendix 2 (Section 16.2) for a detailed list on prohibited concomitant medications

6.2.2.2 Prohibited medication specific to combination arm ruxolitinib + crizanlizumab or ruxolitinib + sabatolimab, or ruxolitinib +NIS793)

In addition to the prohibited medications listed under Section 6.2.2, the following medications are prohibited during the study, including the extension treatment phase for the treatment arms ruxolitinib + crizanlizumab, ruxolitinib + sabatolimab, and ruxolitinib + NIS793:

- Administration of monoclonal antibodies other than crizanlizumab, sabatolimab or NIS793.
- Use of live vaccines after administration of NIS793, crizanlizumab or sabatolimab at any time during the study treatment period until 90 days, 105 days and 150 days after the last dose of NIS793, crizanlizumab and sabatolimab, respectively.

Refer to Table 16-2 in Appendix 2 (Section 16.2) for a detailed list on prohibited concomitant medications.

6.2.2.3 Prohibited medication specific to combination arm ruxolitinib + rineterkib

In addition to the prohibited medications listed under Section 6.2.2, the following medications are prohibited during the study, including the extension treatment phase, or prohibited within a defined time window for the treatment arm ruxolitinib + rineterkib:

- Medication, herbs or supplements that are strong inhibitors of CYP3A4 as rineterkib is metabolized mainly by CYP3A4
- Strong inducers and inhibitors of CYP2C8 as rineterkib is partly metabolized by CYP2C8.

6.2.2.4 Dose reduction of ruxolitinib with concomitant strong CYP3A4 inhibitors or fluconazole

The drug label for ruxolitinib should be consulted for guidance on ruxolitinib dose adjustment requirement when coadministered with strong inhibitors of CYP3A4 or dual inhibitors of CYP2C9 and CYP3A4 (e.g. fluconazole). See Table 16-2 in Appendix 2 (Section 16.2) for a listing of strong CYP3A4 inhibitors. Ruxolitinib is eliminated through metabolism by CYP3A4 and CYP2C9. With concomitant strong CYP3A4 inhibitors such as, but not limited to, ketoconazole, clarithromycin, itraconazole, nefazodone and telithromycin (see Appendix 2, Section 16.2), plasma exposure of ruxolitinib increases approximately 2-fold. Therefore, when the concomitant administration of a strong systemic CYP3A4 inhibitor or a dual inhibitor of CYP2C9 and CYP3A4 is required for patient management the dose of ruxolitinib must be adjusted as follows according to the respective treatment arm.

For ruxolitinib single agent, ruxolitinib + crizanlizumab, ruxolitinib + sabatolimab, or ruxolitinib + NIS793 (Part 1 from start of cycle 3 and parts 2 and 3): Use of strong CYP3A4 inhibitors or fluconazole is strongly discouraged, and investigators should consider alternative therapies wherever possible. However, if the use of a strong CYP3A4 inhibitor is necessary for patient management, then a dose reduction of ~ 50% for ruxolitinib is appropriate, to be administered twice daily.

For ruxolitinib + siremadlin (Part 1 from start of cycle 3 and parts 2 and 3): Concomitant use of strong or moderate inhibitors of CYP3A4/5 are **strictly** prohibited 48 hours before, during and 48 hours after siremadlin administration, as concomitant strong CYP3A4 inhibitors such as itraconazole increase plasma exposure of siremadlin by approximately 6-fold. If the use of a strong CYP3A4 inhibitor is necessary for patient management, the use of a strong CYP3A4/5 inhibitor or fluconazole can only be concomitantly administered outside the aforementioned restriction window (between day 7 and day 26 of a 28 day treatment cycle), and will require a ruxolitinib dose reduction of ~50% to be administered twice daily.NOTE: once the course of therapy using a strong CYP3A4 inhibitor or fluconazole has been completed, the patient may resume his/her prior dose level of ruxolitinib beginning the next day.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (As assigned by Novartis to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the ICF, the subject is assigned to the next sequential Subject No. available.

The investigator or designated staff will contact the Interactive Response Technology (IRT) and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Subject No. must not be reused for any other subject. A new ICF will need to be signed if the investigator chooses to re-screen the subject after a subject has screen failed. If a subject is re-screened or participates again in another part of the study, a new subject ID will

be generated, however, the original subject ID must be added in the respective eCRF to link the two subjects for reporting and validation purposes. All required screening activities must be performed when the subject is re-screened for participation in the study. An individual subject may only be re-screened once for the study. Once the number of subjects screened and allocated/randomized has been reached to ensure the target number of enrolled subjects for the study, Novartis may close the study to further screening. In this case, the subjects who screen failed will not be permitted to re-screen. If the subject fails to be allocated to a treatment (Part 1 subjects) or to be randomized (Part 2 or Part 3) for any reason, the reason will be entered into the appropriate Disposition eCRF.

6.3.2 Treatment assignment, randomization

No randomization will be performed in Part 1 of this study. The assignment of a subject to a particular treatment arm (ruxolitinib + siremadlin, ruxolitinib + crizanlizumab, ruxolitinib + sabatolimab, ruxolitinib + rineterkib or ruxolitinib + NIS793) and dose cohort within the ruxolitinib + siremadlin and ruxolitinib + rineterkib arms will be using the IRT system and coordinated by Novartis.

For Part 2 and Part 3 (randomization parts of the study), following screening and prior to dosing, all eligible subjects will be randomized via IRT to one of the treatment arms open to enrollment (Section 3). The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the subject. A medication number will not be provided for the local supply of ruxolitinib in USA.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. The randomization numbers will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers (except for the local supply of ruxolitinib in USA). A separate medication list will be produced by Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment with the exception of local supply of ruxolitinib in USA for which no medication number will be provided.

Details of the randomization requirements will be documented in randomization requirement specification document. The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

Treatment will be open to subjects, investigator staff, persons performing the assessments, and the clinical trial team (CTT).

6.5 Dose escalation and dose modification

As outlined in Section 3, the proposed RP2D of siremadlin and rineterkib for the combination treatments are not known. Therefore, a dose escalation approach will be used in Part 1 to determine the RP2D as outlined in Section 6.5.1and Section 6.5.2.

For the ruxolitinib + crizanlizumab, the ruxolitinib + sabatolimab, and the ruxolitinib + NIS793 combination treatments the proposed RP2Ds will be confirmed in a safety-run-in rather than using the dose escalation approach.

DLT definitions and dose modification guidelines for all three combinations are provided in Section 6.5.3 and Section 6.5.4, respectively.

6.5.1 Dose escalation guidelines

6.5.1.1 Starting dose

Ruxolitinib as a single agent has been tolerated up to doses of 25 mg BID (Verstovsek et al 2010). From the INCB018424-251 trial and supported by results from the CINC424A2352 study, 15 mg BID and 20 mg BID was established as the most effective and safest starting dose, followed by individualized dose titration. In patients with moderate thrombocytopenia, data show the feasibility of starting with 5 mg BID and then escalating to 10 mg and occasionally to 15 mg BID, without causing severe thrombocytopenia (Cervantes 2014).

As outlined in Section 5 patients must be on a stable ruxolitinib dose for at least 4 weeks prior to first dose of study treatment. A subject's ruxolitinib dose can vary between 5 mg BID and 25 mg BID and it is neither escalated nor de-escalated and will remain fixed at the stable dose during the dose escalation/safety run-in part (Part 1) of the study unless dose modification is required due to toxicity as outlined in Section 6.5.4.

The rationale for the regimen for siremadlin in combination with ruxolitinib is discussed in Section 4.2.1. To mitigate the risk of adverse events, the starting dose of siremadlin is 20 mg/day (day 1-5 each of a 28-day cycle). This dose was chosen based on prior single agent safety data in subjects with solid and hematological malignancies and it is supported by population PK/PD modeling of thrombocytopenia and bone marrow blast (AML subjects) data (CHDM201X2101). The starting dose corresponds to ~3.15-fold reduction compared to the cumulative dose of siremadlin single agent RD, as evaluated in CHDM201X2101 at 45 mg/day (day 1-7 of a 28-day cycle), or 315 mg/cycle. At the starting dose level, limited target myelosuppression is predicted, while clinical activity is already expected. Additionally, PBPK SimCyp modeling of siremadlin in combination with ruxolitinib, at their respective dose and treatment schedules, did not predict any clinically relevant PK DDI (see Section 4.2.1). For crizanlizumab the dose level chosen to be evaluated in this trial is 5 mg/kg IV infusion (with a second loading dose after 14 days of initial dosing for Cycle 1 only), every 4 weeks cycle. This dose based on p-Selectin inhibition of SelG1 evaluated in healthy subjects, as well as the acceptable safety data observed in the Phase I CSEG101A2101 study. This dose was also evaluated in the Phase II CSEG101A2201 study, with 67 patients receiving SelG1 at 5 mg/kg (Ataga et al 2017).

For sabatolimab the dose level chosen to be evaluated in this trial is 800 mg IV infusion Q4W. This dose is based on acceptable safety, as well as efficacy, PK and target (TIM-3) occupancy evaluated in CMBG453X2101 and CPDR001X2105 trials for sabatolimab.

The rationale for the regimen for rineterkib in combination with ruxolitinib is discussed in Section 4.2.4. The starting dose of rineterkib is 200 mg QD and was chosen based on prior single agent safety data in subjects with solid malignancies (CLTT462X2101). The starting dose corresponds to ~2-fold reduction compared to the MTD (400 mg QD) of rineterkib single agent, as evaluated in CLTT462X2101. Additionally, PBPK SimCyp modeling of rineterkib in combination with ruxolitinib, at their respective dose and treatment schedules, did not predict any clinically relevant PK DDI.

For NIS793 the dose level chosen to be evaluated in this trial is 2100 mg IV infusion Q3W. This dose is based on acceptable safety, as well as efficacy and PK/PD modeling information from the CNIS793X2101 study investigating NIS793 in combination with PDR001 (spartalizumab) in advanced solid tumors.

6.5.1.2 Provisional dose levels

Table 6-2 and Table 6-3 describes the starting dose and the dose levels that may be evaluated during this trial for siremadlin and rineterkib, respectively.

Table 6-2 Provisional dose levels for siremadlin

Dose Level	Proposed Daily Dose*	Increment From Previous Dose
- 1**	10 mg	- 50%
1	20 mg	(starting dose)
2	30 mg	50%
3	40 mg	33%
*Additional and/or intermediate dose levels may be added during the course of the study. Cohorts may be added at any dose level below the MTD in order to better understand safety, PK, or PD. **Dose level -1 represents a dose that may be evaluated if de-escalation from the starting dose is required due to toxicity		

Table 6-3 Provisional dose levels for rineterkib

Dose Level	Proposed Daily Dose*	Increment From Previous Dose
- 1**	100 mg	- 50%
1	200 mg	(starting dose)
2	300 mg	50%
*Additional and/or intermediate dose levels may be added during the course of the study. Cohorts may be added at any dose level below the MTD in order to better understand safety, PK, or PD. **Dose level -1 represents a dose that may be evaluated if de-escalation from the starting dose is required due to toxicity.		

6.5.2 Guidelines for dose escalation and determination of RP2D

The maximum tolerated dose (MTD) is the highest drug dosage that is not expected to cause dose-limiting toxicity (DLT) in more than 33% of the treated subjects during the DLT evaluation period. The recommended Phase 2 dose (RP2D) may be chosen with fewer subjects, prior to identification of the MTD and may be lower than the MTD.

Siremadlin and rineterkib

For the purpose of dose escalation decisions and determination of RP2D, each cohort in Part 1 of the study will consist of 3 to 6 newly enrolled subjects who will be treated at the specified dose levels. Subjects in the first cohort of siremadlin combined with ruxolitinib will be treated with the starting dose of siremadlin 20 mg QD (Day 1-5 of each 28-day cycle). Subjects in the first cohort of rineterkib combined with ruxolitinib will be treated with the starting dose of rineterkib 200 mg QD.

Subjects must complete a minimum of two cycles of treatment with the minimum safety evaluation and drug exposure (see Section 12.1.3 for details) or have had a DLT within the DLT period to be considered evaluable for dose escalation decisions. Dose escalation decisions and RP2D will occur when the cohort of subjects has met these criteria. If a minimum of 3 subjects are required in a cohort and only 2 of these subjects are evaluable and neither subject has experienced a treatment-related toxicity > CTCAE grade 1, dose escalation decisions may be considered.

Dose escalation decisions will be made by Investigators and Novartis study personnel. Decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study including safety information, DLTs, all CTCAE Grade ≥ 2 toxicity data during Cycle 1 or 2, PK, and PD data from evaluable subjects. The recommended dose for the next cohort of subjects will be guided by the Bayesian logistic regression model (BLRM) with EWOC principle. A subject's ruxolitinib dose is neither escalated nor de-escalated and will remain fixed at the stable dose during the dose-escalation/safety run-in part (Part 1) of the study.

The adaptive Bayesian methodology provides an estimate of all dose levels of the combination agent, which is escalated, that do not exceed the MTD and incorporates all DLT information at all dose levels for this estimation. In general, the next dose will have the highest chance that the DLT rate will fall in the target interval (16-33%) and will always satisfy the EWOC principle. In all cases, the dose for the next cohort will not exceed a 100% increase from the previous dose. Smaller increases in dose may be recommended by the investigators and sponsor upon consideration of all of the available clinical data.

If the first 2 subjects in a cohort experience a DLT, further enrollment to that cohort will stop and the BLRM will be updated with this new information. Re-evaluation of the available safety, PK, and PD data will occur. By incorporating information gained at the preceding dose levels, additional subjects may be enrolled at this dose level or a lower dose level as agreed by Investigators and Novartis personnel and if the BLRM predicts that the risk that this dose exceeds the MTD remains below 25% (EWOC).

Dose escalation will continue until identification of the MTD or a suitable lower RP2D. This will occur when the following conditions are met:

- at least 6 subjects have been treated at this dose and observed for two cycles
- this dose satisfies one of the following conditions:
    1. the posterior probability of targeted toxicity at this dose exceeds 50% and is the highest among potential doses, or
    2. Minimum of 12 subjects have already been treated on the trial.

- It is the dose recommended for subjects, either per the model or by review of all clinical data by Novartis and investigators in a dose escalation teleconference, see Section 6.5.2.1.

To better understand the safety, tolerability and PK of siremadlin or rineterkib in combination with ruxolitinib, additional cohorts of subjects may be enrolled at preceding dose levels, or to intermediate dose levels before or while proceeding with further dose escalation.

If a decision is made to escalate to a higher dose level but one or more additional subject(s) treated at the preceding dose level experiences a DLT during the first cycle of treatment, then the BLRM will be updated with this new information before any additional subjects are enrolled at that higher dose level. Subjects ongoing will continue treatment at their assigned dose levels.

Crizanlizumab, sabatolimab and NIS793

For crizanlizumab, the dose level chosen to be evaluated in Arm 2 will be 5 mg/kg IV infusion Q4W (with the 2nd loading dose after 14 days of initial dosing for Cycle 1 only). For sabatolimab, the dose level chosen to be evaluated in Arm 3 will be 800 mg IV Q4W. For NIS793, the dose level chosen to be evaluated in Arm 5 will be 2100 mg IV Q3W. If 2 subjects in any safety run-in arm (either Arm 2, Arm 3, or Arm 5) in Part 1 of the study experience a DLT within the first 2 cycles of study treatment, further enrollment into that arm will stop and that combination treatment will not open in Part 2.

A decision may be made to include further subjects into the combination arm or conduct additional dose cohorts within the arm based on a synthesis of all relevant data available in the ongoing study including safety information, DLTs, all CTCAE Grade ≥ 2 toxicity data during Cycle 1 or 2, PK, and PD data from evaluable subjects. Any decisions will be made by Investigators and Novartis study personnel.

For Japan only: Further subjects can be added after the RP2D has been determined to further characterize safety.

6.5.2.1 Implementation of dose escalation decisions

To implement dose escalation decisions for siremadlin and rineterkib in combination with ruxolitinib, the available toxicity information (including adverse events and laboratory abnormalities that are not DLTs), the recommendations from the BLRM, and the available PK and PD information will all be evaluated by the Investigators and Novartis study personnel (including the study physician and statistician) during a dose decision meeting by teleconference. Drug administration at the next higher dose level may not proceed until the investigator receives written confirmation from Novartis indicating that the results of the previous dose level were evaluated and that it is permissible to proceed to a higher dose level.

6.5.2.2 Intra-Subject dose escalation

Intra-subject dose escalation is not allowed in this study.

6.5.3 Definitions of dose limiting toxicities (DLTs)

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as clinically significant and considered by the Investigator to be related to siremadlin,

crizanlizumab, sabatolimab, rineterkib, NIS793 as single contributors or in combination with ruxolitinib, that occurs within the first two cycles of treatment (C1D1 through to C3D1) of Part 1 and meets any of the criteria included in Table 6-4. Toxicities that are related to MF, MF progression, inter-current illness, or concomitant medications that occurs within the first two cycles of treatment (C1D1 through to C3D1) with ruxolitinib + siremadlin or ruxolitinib + crizanlizumab or ruxolitinib + sabatolimab or ruxolitinib + rineterkib or ruxolitinib + NIS793 will not be considered a DLT. The National Cancer Institute Common Terminology Criteria for Adverse events (NCI CTCAE) version 5.0 will be used for all grading. For the purpose of dose escalation decisions for the ruxolitinib + siremadlin and ruxolitinib + rineterkib combination treatments, DLTs will be considered and included in the BLRM.

The investigator must notify the sponsor immediately of any unexpected CTCAE grade ≥ 3 adverse events or laboratory abnormalities. Prior to enrolling subjects into a higher dose level, CTCAE grade ≥ 2 adverse events will be reviewed for all subjects at the current dose level.

Table 6-4 Criteria for defining dose-limiting toxicities (related to study treatment)

Toxicity	DLT Criteria
Hematologic toxicities	Acute severe myelosuppression in absence of leukemic transformation: Neutropenia G4* Febrile neutropenia G ≥ 3 (ANC < 1.0 x 10^9/L + Fever ≥ 38.5 degrees C) Thrombocytopenia G4* (platelets < 25 x 10^9/L) persisting ≥ 3 days Prolonged myelosuppression in absence of leukemic transformation: Thrombocytopenia G3 (platelets < 50 x 10^9/L) persisting ≥ 21 days Thrombocytopenia G3 (platelets < 50 x 10^9/L) prior to dosing on C2D1 and C3D1 **
Non-hematologic toxicities	All toxicity ≥ Grade 3 not due to underlying MF or complications of the disease (for all arms)
	Other Toxicity < Grade 3 considered as DLTs for subjects on arms containing rineterkib: • Retinal vein occlusion of any CTCAE Grade confirmed by ophthalmologic evaluation • Newly emerging grade 2 total bilirubin with ≥ CTCAE Grade 2 AST/ALT
	Other Toxicity < Grade 3 considered as DLTs for subjects on arms containing NIS793: • Grade 2 bullous disease that does not resolve to ≤ Grade 1 within 7 days of starting corticosteroids
* in two consecutive assessments within 24 hours (the second assessment will be considered valid and final) **in case of platelets count of 40-50 x 10^9/L, the assessment has to be repeated within 24 hours. The second assessment will be considered valid and final CTCAE version 5.0 will be used for all grading	

6.5.4 Dose modifications

For subjects who do not tolerate the protocol-specified dosing schedule due to DLT or other toxicities, dose adjustments are permitted in order to allow subjects to continue the study treatment. Similar guidelines also apply to the extension treatment phase. All dose modifications should be based on the worst preceding toxicity and AEs are to be graded

according to NCI CTCAE v5.0. If the investigational study treatment is being held due to toxicity, planned visits and all assessments should continue as scheduled, except without dosing.

For Part 1, dose modifications for toxicities occurring during the DLT-definition period (i.e. first 2 cycles of treatment C1D1 through C3D1), and considered as treatment-related, will not be allowed unless the toxicity qualifies as DLT. After a toxicity has been characterized as a DLT, a subject can resume therapy with a modified dose according to the guidelines.

During part 2 and 3, investigator should follow the dose modifications for toxicities during any cycle of the treatment period.

These dose changes must be recorded on the appropriate eCRF.

[redacted]

For clinical management of suspected immune-related events for sabatolimab and NIS793, reference to consensus management guidelines is recommended, such as those provided in the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities (NCCN Guidelines for specific populations), ASCO clinical practice guideline for Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy (Brahmer et al 2018) or the ESMO Clinical Practice Guidelines for Management of Toxicities from Immunotherapy (Haanen et al 2017). Note that in general, sabatolimab or NIS793 should be interrupted for grade 3 and 4 toxicities and for a subset of lower grade toxicities. If the specific adverse event is not listed, the guideline for "Other adverse events" must be followed. Deviations to mandatory dose interruptions and/or reductions are not allowed. Permanent treatment discontinuation is mandatory for specific events [redacted]

The investigator should follow the dose modifications for the study drug suspected to be related to the event:

- If the event is suspected to be related to ruxolitinib, the investigator should follow the dose modification specific to ruxolitinib as per current label. If the event is suspected to be related to siremadlin, crizanlizumab, sabatolimab, rineterkib or NIS793, the investigator should follow the dose modifications specific for the suspected study drug. [redacted]
- In the occurrence of potentially overlapping toxicity or if it cannot be distinguished which of the study drugs within the combination is suspected to be related to the event, the investigator should first modify the dose of siremadlin, crizanlizumab, sabatolimab, rineterkib or NIS793 before changing the ruxolitinib dose. If the toxicity does not resolve until the next planned dose of siremadlin, crizanlizumab, sabatolimab, rineterkib or NIS793, the investigator should follow the dose modifications specific to both study drugs within the combination treatment.

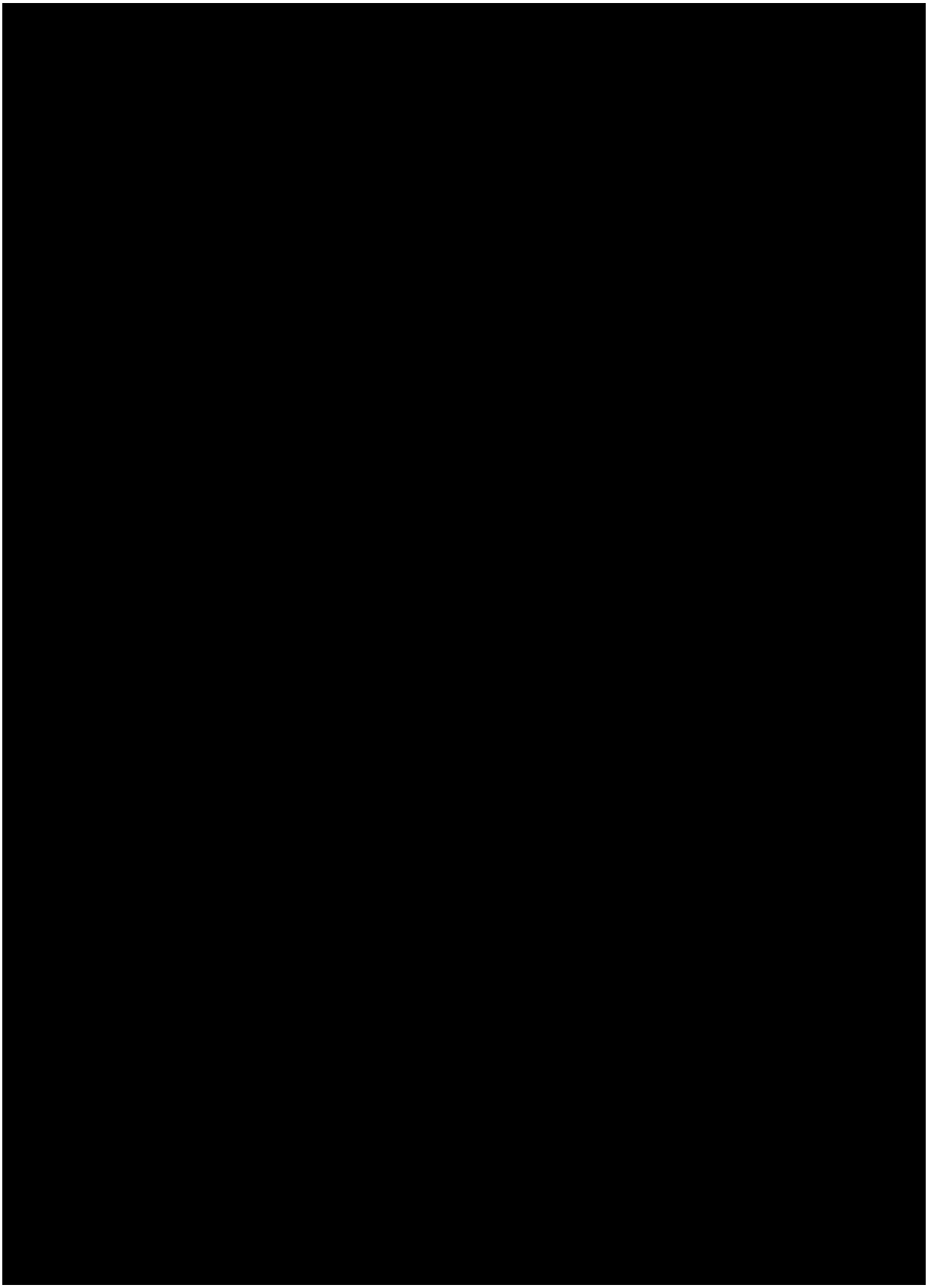
Additionally, the following guidelines need to be considered for patients on siremadlin and rineterkib:

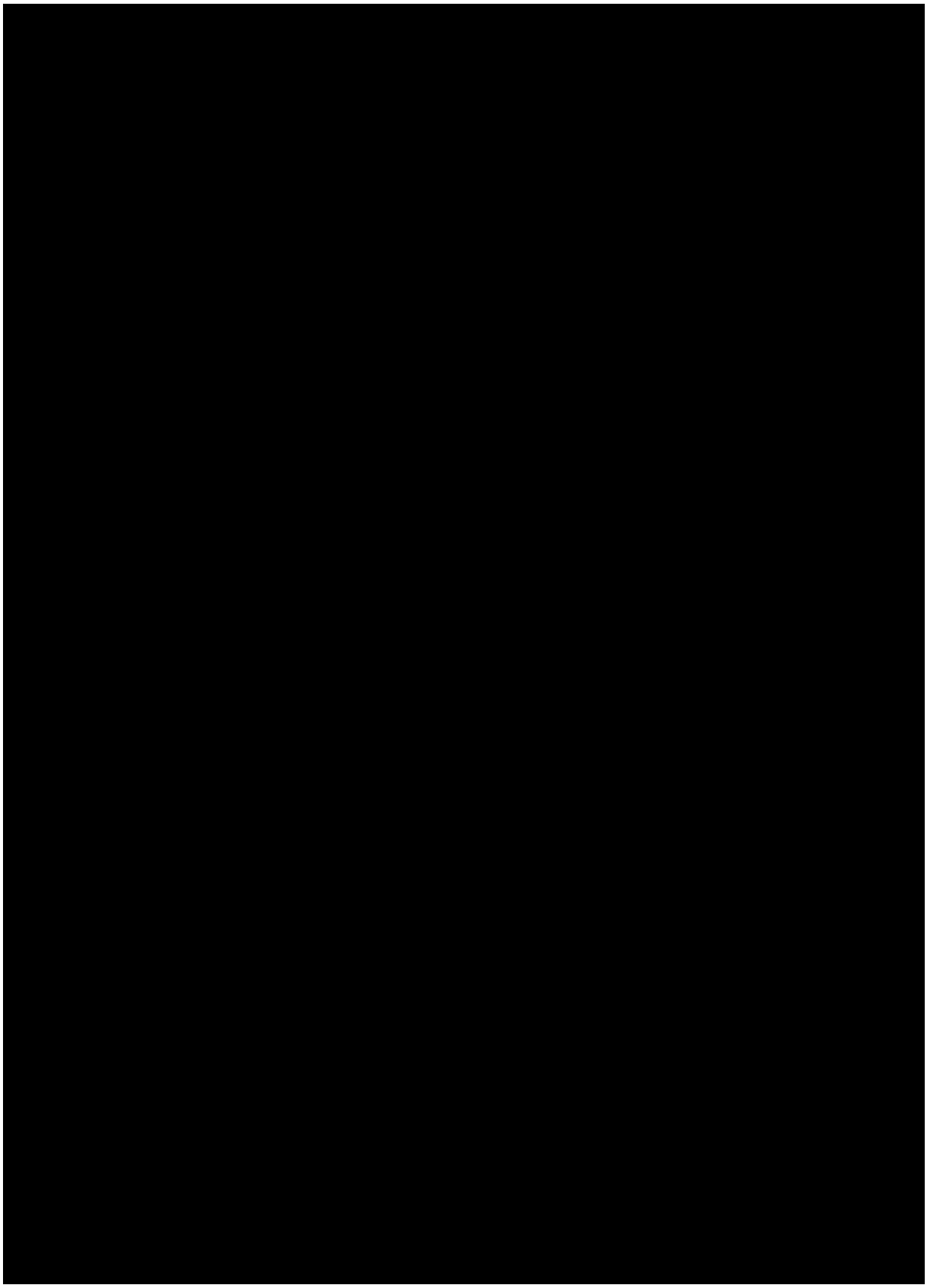
- [redacted] All dose modifications should be based on the worse preceding toxicity (CTCAE v 5.0).
- A patient must discontinue treatment with siremadlin or rineterkib if, after treatment is resumed at a lower dose, the toxicity recurs with the same or worse severity, unless in the opinion of the investigator it is in the patient's best interest to continue siremadlin or rineterkib, and upon documented agreement with Novartis.
- For each patient, once a dose reduction has occurred, the dose level must not be re-escalated during subsequent treatment cycles with siremadlin or rineterkib.

Finally, the following guidelines should be followed for patients on NIS793:

- No dose reductions are allowed for NIS793. Reducing dosing frequency is allowed under circumstances [redacted]
- Dose interruption due to toxicities is permitted. Dosing of study treatment may resume once the AE has resolved, [redacted]

[redacted]





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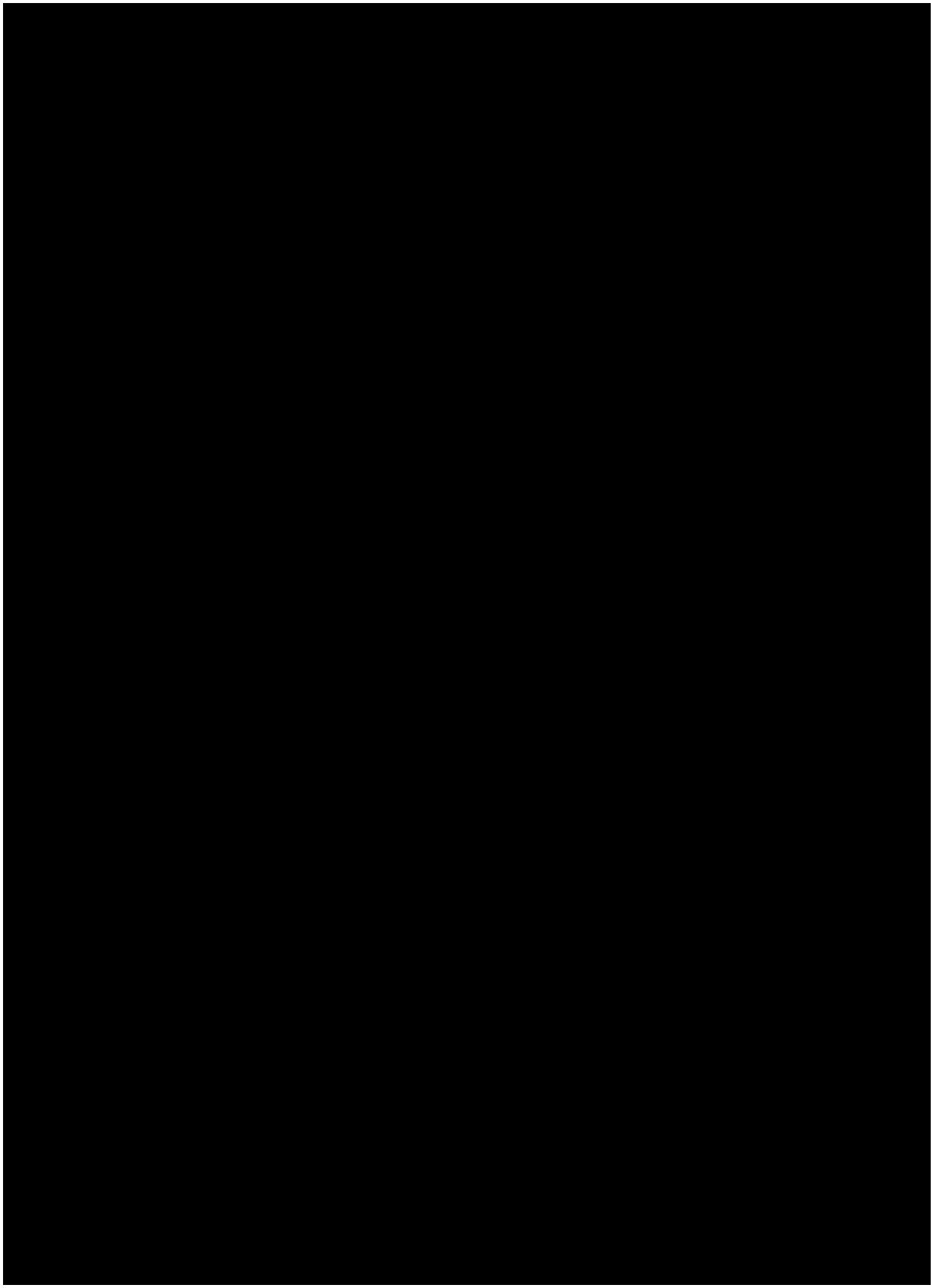

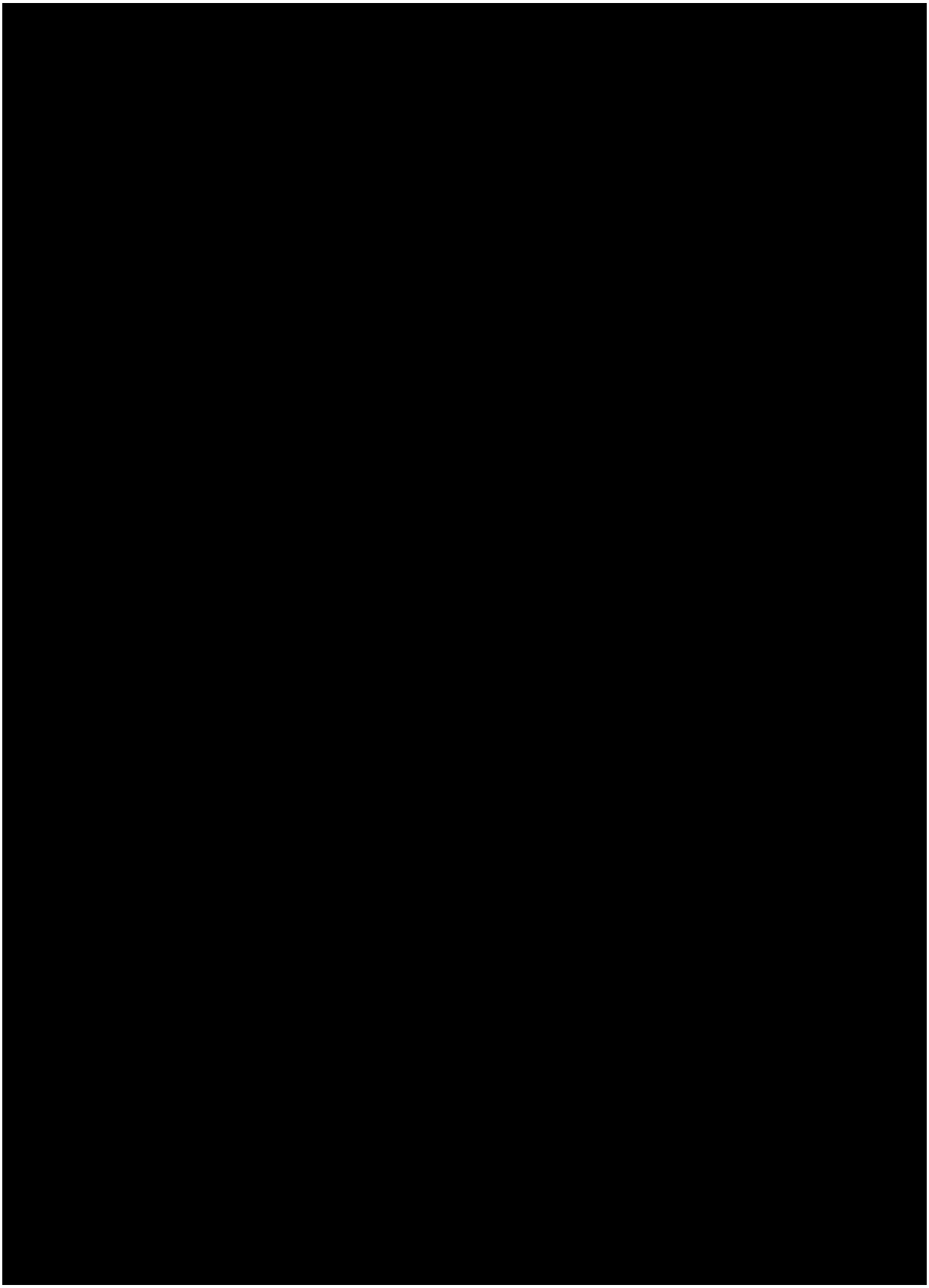

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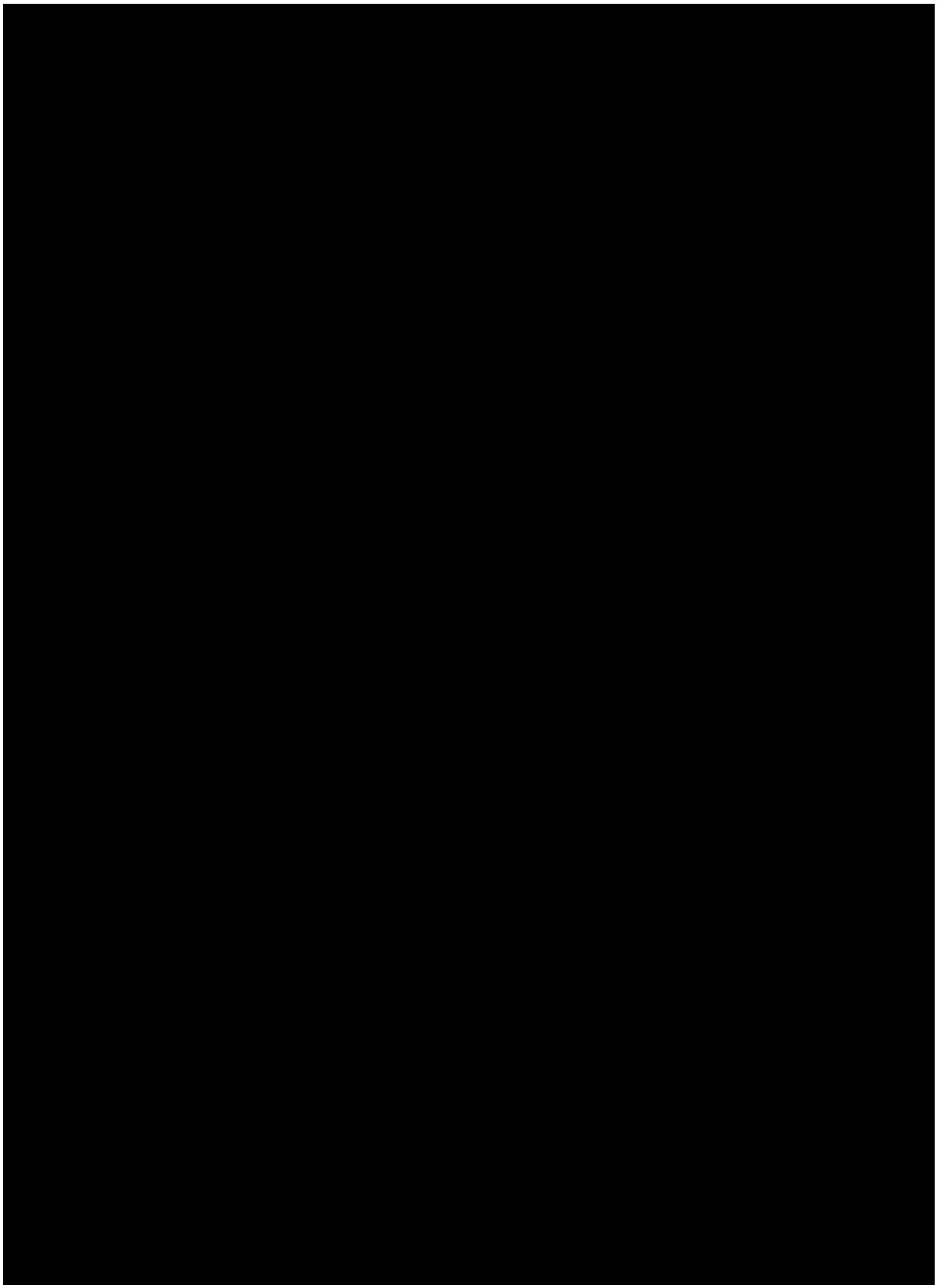

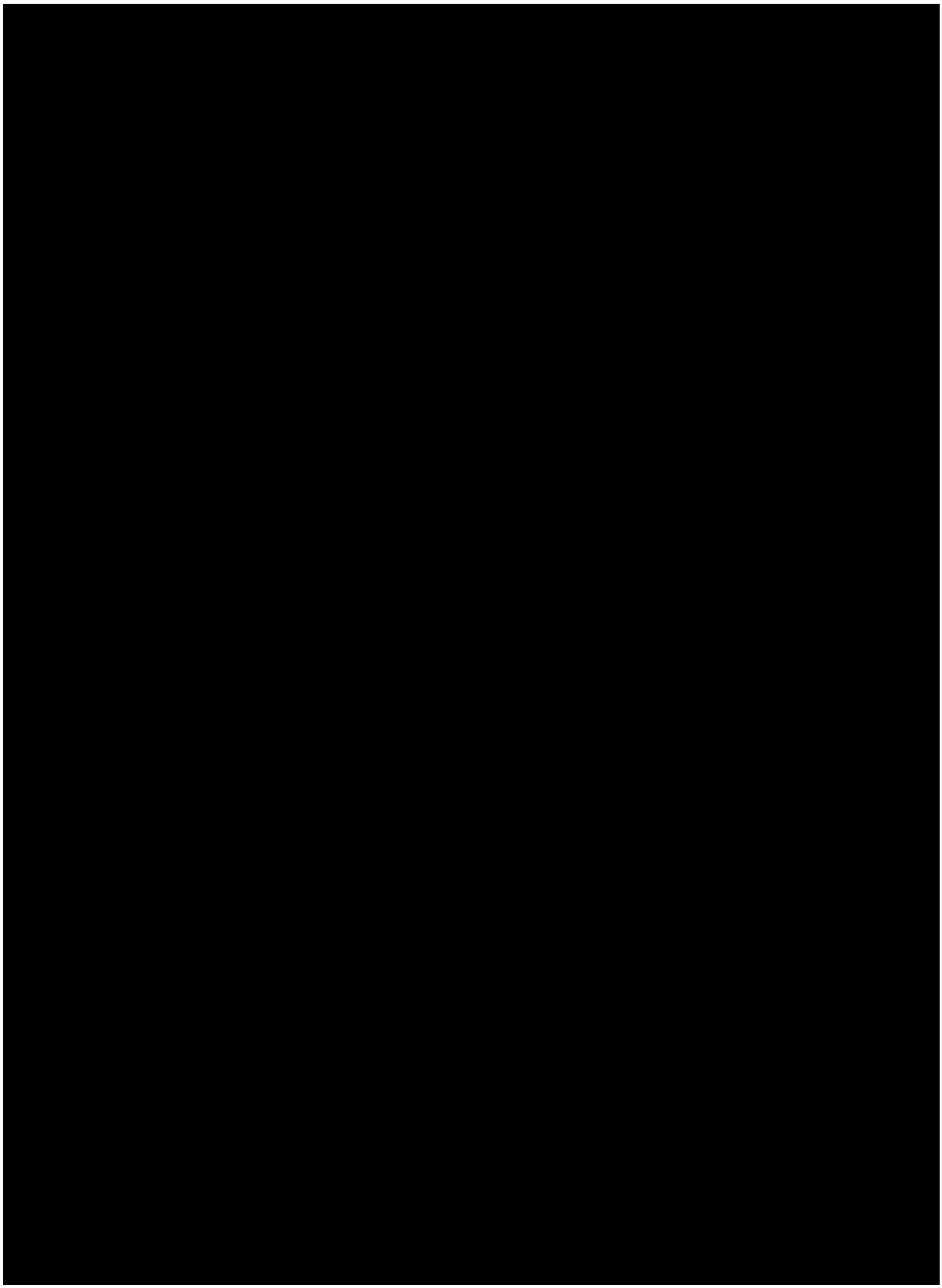

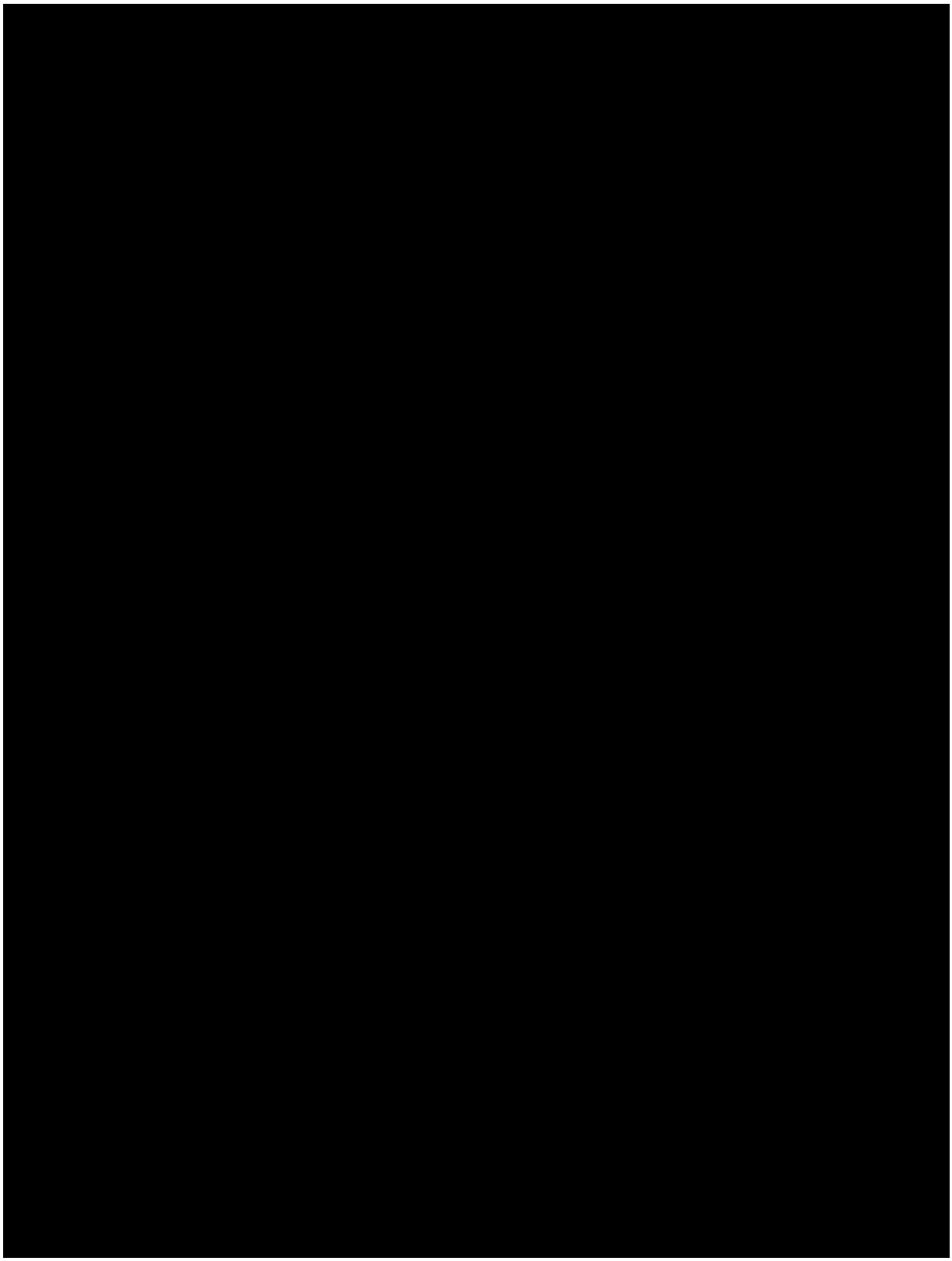

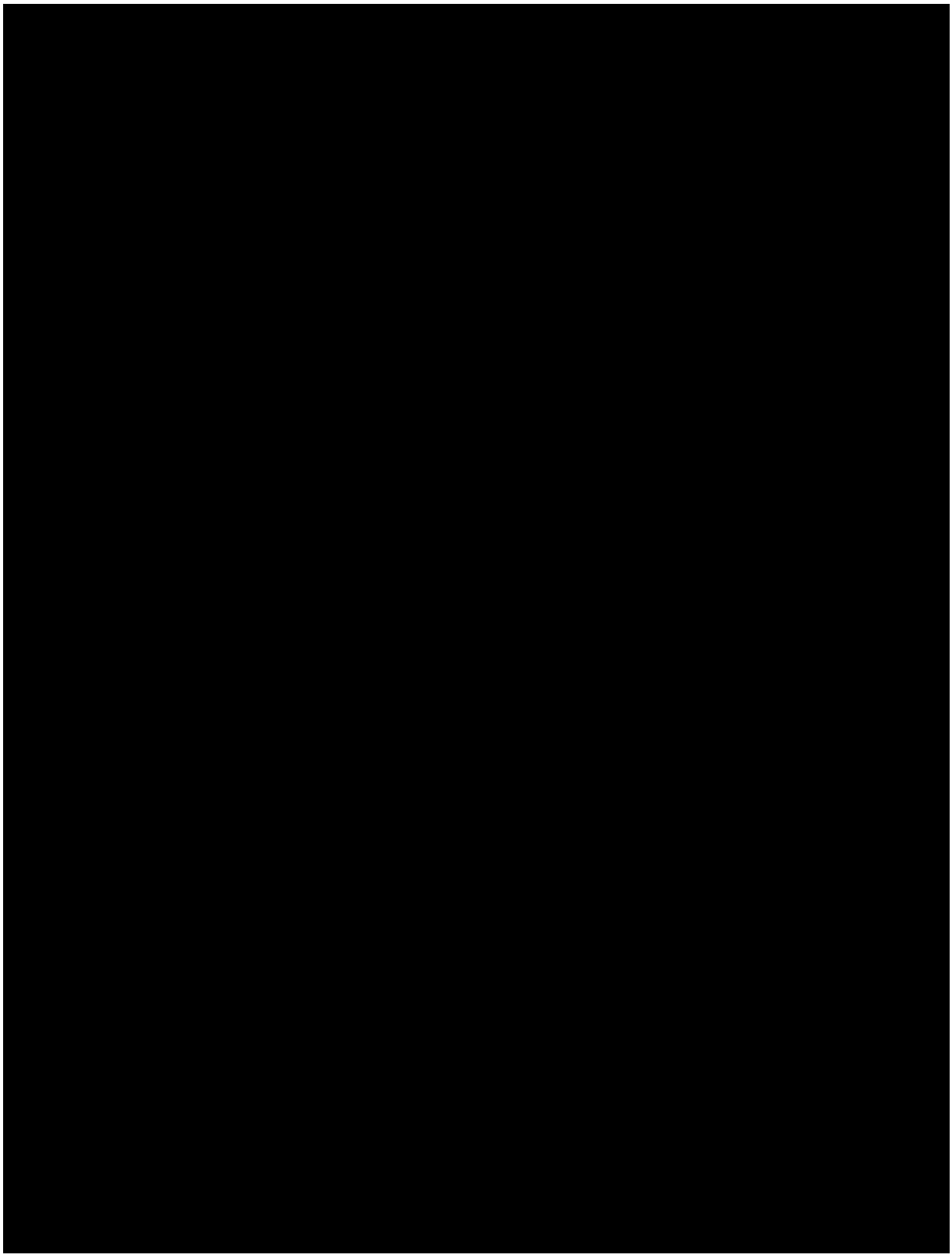

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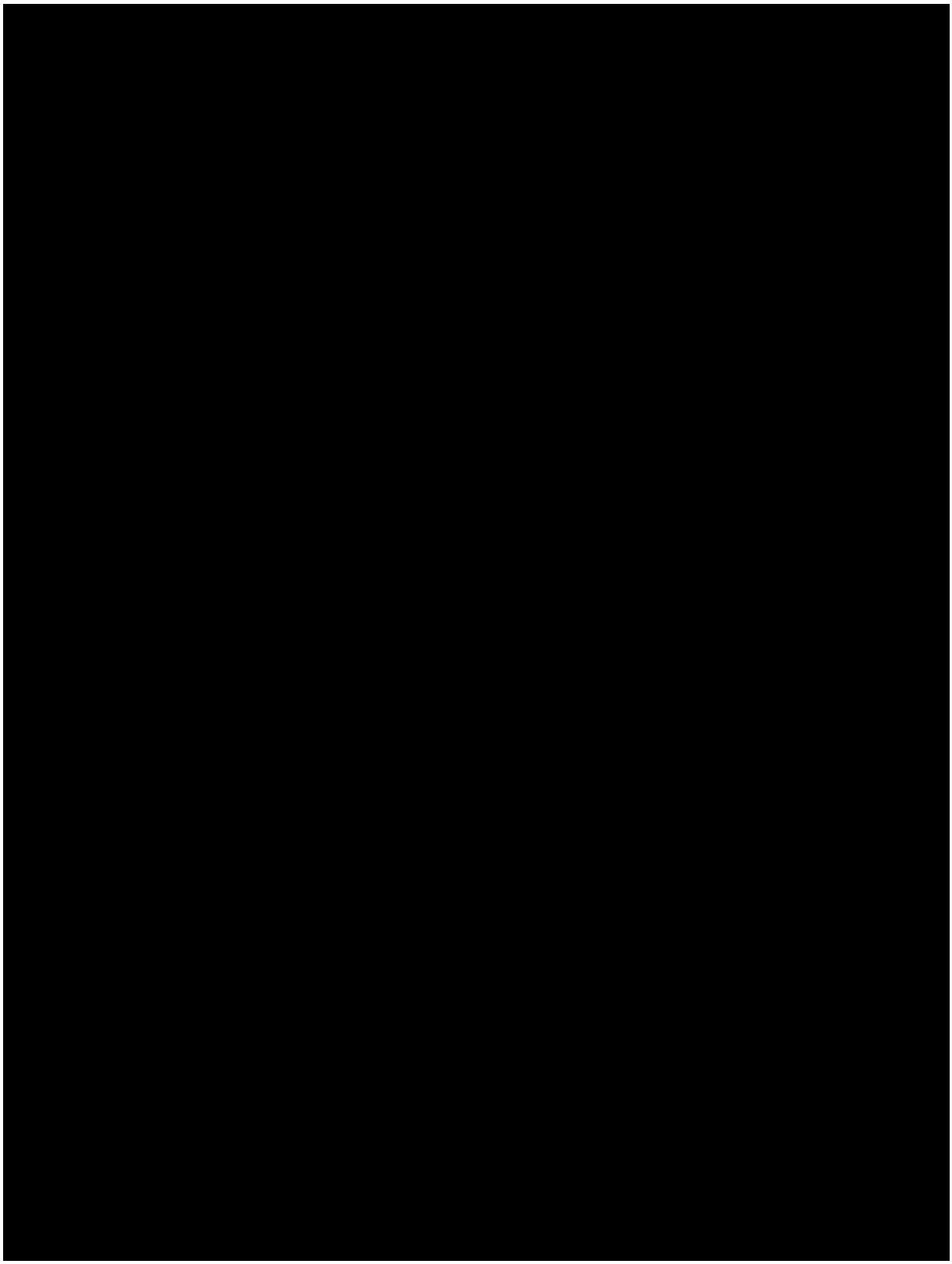
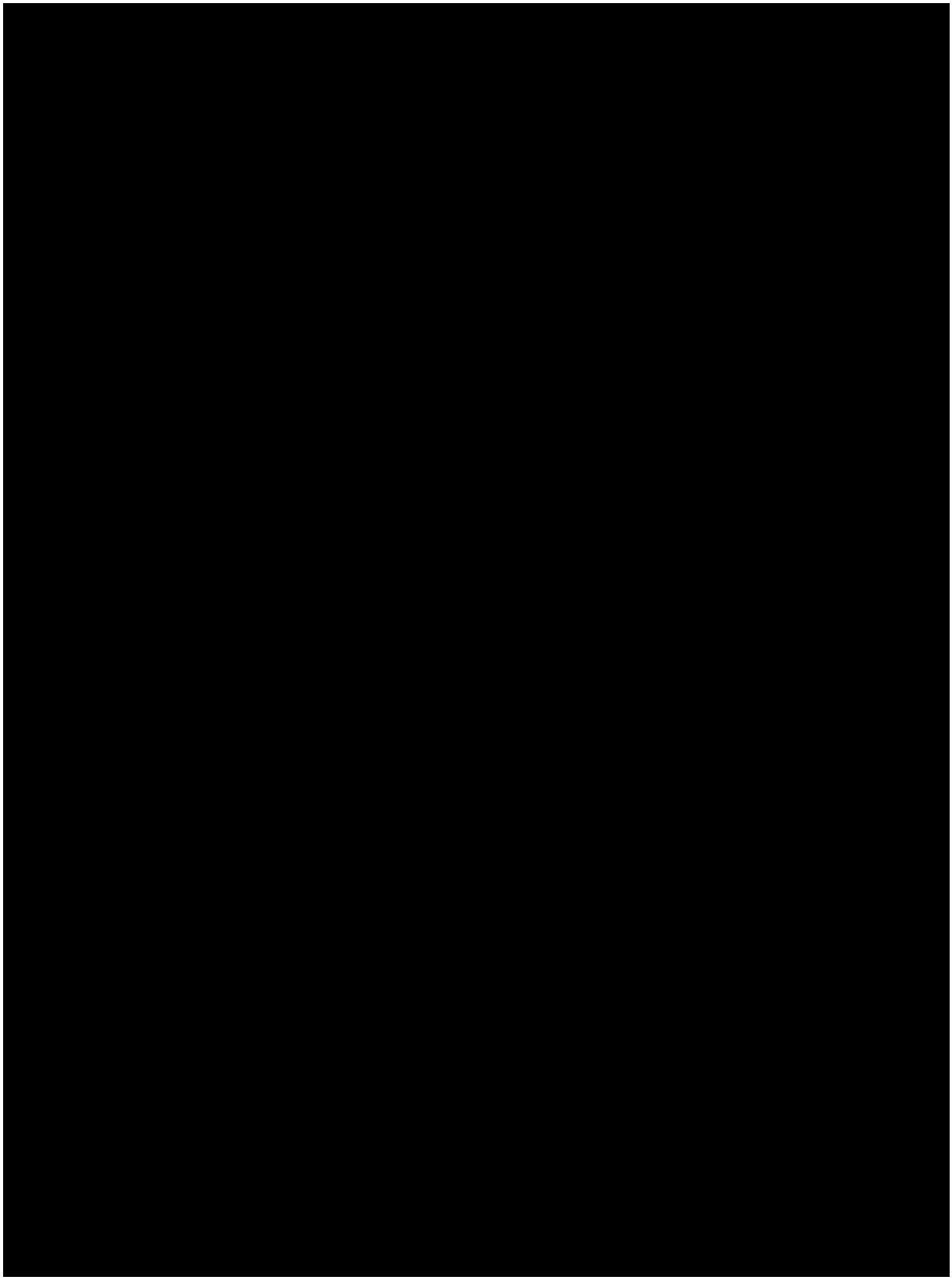
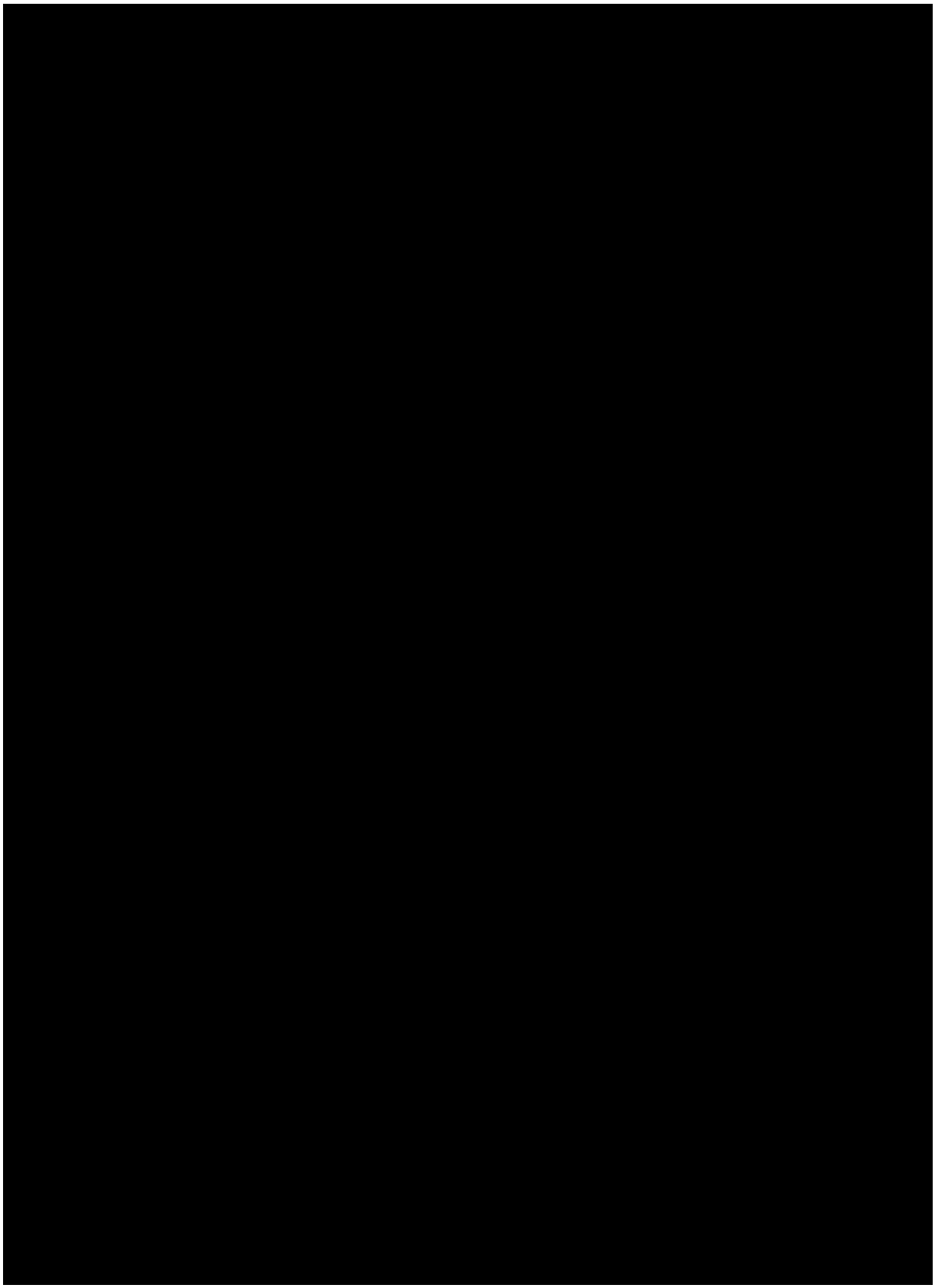
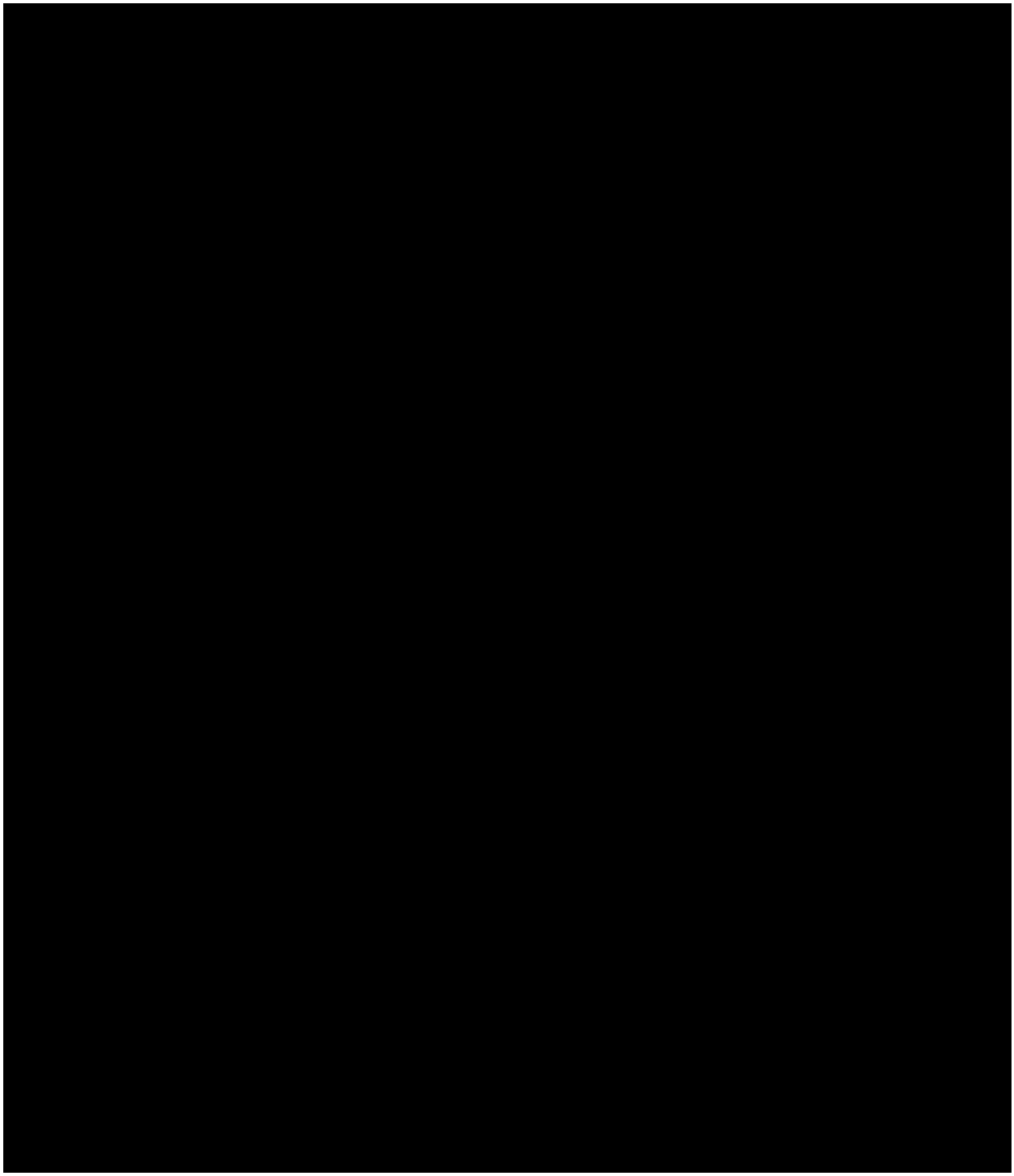








6.5.4.1 Dose adjustments for QTcF prolongation

In case QTcF prolongation > 500 msec (or QTcF prolongation > 60 msec from baseline) is observed at any time point during study treatment, and confirmed, increased ECG safety monitoring is mandatory during or in-between subsequent visits (e.g. collecting ECGs at following treatments at predose and at Cmax), as follows:

- Collect triplicate ECG and confirm QTc assessment (by site cardiologist or Novartis cardiologist)
- Correct any serum electrolyte abnormalities (in particular hypokalemia, hypomagnesemia) before continuing study treatment.
- Review concomitant medication use for other causes for QT prolongation *(refer to qtdrugs.org for known QT prolonging drugs)* and for drugs with the potential to increase the risk of drug exposure related QT prolongation *(e.g. concomitant use of CYP3A4 inhibitors, if the study treatment is a CYP3A4 substrate)*
- Check the dosing schedule and treatment compliance
- Consider collecting a time-matched PK sample *(Refer to PK sampling section for correct procedures)* and record time and date of last study treatment intake. Not applicable during the extension treatment phase.

6.5.5 Follow-up for toxicities

Subjects whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Similar guidelines apply during the extension treatment phase. Appropriate clinical experts such as cardiologist, dermatologist, psychiatrists, etc., should be consulted as deemed necessary. All subjects must be followed up for adverse events and serious adverse events (SAEs) for 30 days after the last dose of single-agent ruxolitinib (control/monotherapy), for 30 days after the last dose of ruxolitinib or siremadlin for subjects on ruxolitinib + siremadlin (or siremadlin monotherapy in Part 3), for 30 days after the last dose of ruxolitinib or rineterkib for subjects on ruxolitinib + rineterkib (or rineterkib monotherapy in Part 3), for 90 days after the last dose of NIS793 for subjects on ruxolitinib + NIS793 (or NIS793 monotherapy in Part 3), for 105 days after the last dose of crizanlizumab for subjects on ruxolitinib + crizanlizumab (or crizanlizumab monotherapy in Part 3), and for 150 days after the last dose of sabatolimab for subjects on ruxolitinib + sabatolimab (or sabatolimab monotherapy in Part 3).

6.5.5.1 Follow up for Siremadlin

For subjects receiving siremadlin, Table 6-10 outlines the follow-up evaluations recommended for toxicities of specific types and CTCAE grades.

Table 6-10 Follow-up evaluations for selected toxicities

Toxicity	Follow-up Evaluation
Blood and lymphatic system disorders	Test twice weekly until ≤ CTCAE grade 2, then restart treatment [redacted] Continue to test weekly until resolution to baseline or stabilization.
Investigations (hematologic) Neutropenia ≥ CTCAE grade 3	Test twice weekly until ≤ CTCAE grade 2, then restart treatment [redacted] Continue to test weekly until resolution to baseline or stabilization. Perform physical examination for check on bruising in case of major thrombocytopenia.

Toxicity	Follow-up Evaluation
Thrombocytopenia ≥ CTCAE grade 3	
Investigations (metabolic) Amylase or lipase ≥ CTCAE grade 3	Test twice weekly until ≤ CTCAE grade 2, then restart treatment [redacted] Continue to test weekly until resolution to ≤ CTCAE grade 1 or stabilization. A CT scan or equivalent imaging procedure to assess the pancreas, liver, and gallbladder is recommended within 7 days of the first occurrence of any ≥ CTCAE grade 3 result, to exclude disease progression or potential other liver disease. In subjects with serum triglycerides ≥ 500 mg/dL, urine amylase also needs to be tested.
Cardiac disorders QT and ECG ECG changes indicative of ischemic event	Refer to ECG and QTc Clinical Safety Standards Guidelines Twice weekly ECGs until normalization or stabilization of ECG findings then restart treatment refer to section 6.5.4.1.

6.5.5.2 Follow up for sabatolimab & NIS793

The emergence of Immune-Related AE (irAE) may be anticipated based on general experience in clinical studies with similar class of compounds that block the negative immune regulators.

An irAE is a clinically significant AE affecting any organ that is associated with study drug exposure, is consistent with an immune-mediated mechanism, and where alternative explanations have been investigated and ruled out or are considered unlikely.

Subjects should be monitored carefully for any skin toxicity or mucositis and study treatment should be discontinued for any suspected case of SJS/TEN.

Serologic, histologic and immunological assessments should be performed as deemed appropriate by the Investigator, to verify the immune-related nature of the AE.

All subjects with signs or symptoms of irAEs should be monitored and managed following the consensus guidelines from NCCN, ASCO or ESMO for the management of immune-related adverse events as outlined in Section 6.5.4

Patients whose treatment is interrupted or permanently discontinued due to an irAE, AE or clinically significant laboratory value, must be followed-up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary.

In case of a suspected irAE, the relevant immunological assessments (e.g. rheumatoid factor, anti-DNA Ab, etc.) should be performed. In case of a toxicity suspected to be a cytokine release syndrome, the assessments outlined in Section 8 (Table 8-2, Table 8-3, Table 8-4 & Table 8-5) must be performed. All patients must be followed up for irAEs, AEs and SAEs for 90 days following the last dose of NIS793 in combination with ruxolitinib, and for 105 days following the last dose of sabatolimab in combination with ruxolitinib.

[redacted] For any AE/AEs Grade 1 and/or Grade 2, treatment with sabatolimab should be maintained at the determined dose and schedule, unless otherwise specified in Table 6-7. Similarly, [redacted]

[redacted] For any AE/AEs Grade 1 and/or Grade 2, treatment with NIS793 should be maintained at the determined dose and schedule, unless otherwise specified in [redacted]

6.5.5.3 Follow up on potential drug-induced liver injury (DILI) cases

Subjects with transaminase increase combined with TBIL increase may be indicative of potential DILI and should be considered as clinically important events.

The threshold for potential DILI may depend on the subject's baseline AST/ALT and TBIL value; subjects meeting any of the following criteria will require further follow-up as outlined below:

- For subjects with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For subjects with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2 in subjects without bone metastasis, or elevation of ALP liver fraction in subjects with bone metastasis.

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury.

In the absence of cholestasis, these subjects should be immediately discontinued from study treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment, and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR, and alkaline phosphatase.
2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, and history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Obtain PK sample, as close as possible to last dose.
5. Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant," (Table 6-11) and thus, meet the definition of SAE and should reported as SAE using the term "potential drug-induced liver injury." All events should be followed up with the outcome clearly documented.

Table 6-11 Guidance to rule out possible alternative causes of observed LFT abnormalities

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• Antinuclear Antibodies (ANA) & Anti-Smooth Muscle Antibody (ASMA) titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, GGT, Mean Corpuscular Volume (MCV), CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic congestive heart failure, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, Endoscopic retrograde cholangiopancreatography (ERCP) as appropriate.
Wilson disease (if <40 yrs old)	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

Other causes should also be considered based upon participants' medical history (hyperthyroidism / thyrotoxic hepatitis – T3, T4, TSH; cardiovascular disease / ischemic hepatitis – ECG, prior hypotensive episodes; Type 1 diabetes / glycogenic hepatitis).

Following appropriate causality assessments, as outlined above, the causality of the treatment is estimated as "probable" i.e. >50% likely, if it appears greater than all other possible causes of liver injury combined. The term "treatment-induced" indicates *probably caused* by the treatment, not by something else, and only such a case can be considered a DILI case and should be reported as an SAE.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant," and thus, meet the definition of SAE and should be reported as SAE using the term "potential treatment-induced liver injury." All events should be followed up with the outcome clearly documented.

6.6 Additional treatment guidance

Tumor Lysis Syndrome (TLS) TLS was observed in subjects diagnosed with hematological malignancies (AML) and administered siremadlin in study CHDM201X2101 with siremadlin. One subject, who had grade 4 TLS, was treated according to regimen 2C (daily dosing Day 1-7, Q4W) at 45 mg siremadlin dose. During this study, including the extension treatment phase, subjects receiving siremadlin should be closely monitored (including relevant laboratory tests) for signs and symptoms of TLS before initiation and during a treatment cycle. Risk assessment of TLS, prophylaxis and events should be managed according to the institutional guidelines.

Before initiation of a treatment cycle and during a treatment cycle, the following measures should be followed:

Before initiation of a treatment cycle:

- Prophylaxis (i.e. allopurinol) for TLS should be administered.
- Oral fluids are recommended
- Prompt supportive care in case of acute TLS (IV fluids and rasburicase as clinically indicated, when uric acid continues to rise despite allopurinol/febuxostat and fluids)

During a treatment cycle:

- Frequent monitoring of the following laboratory tests (per Table 8-2 and Table 8-3 and as clinically indicated): potassium, phosphorus, calcium, creatinine, and uric acid
- Encourage oral hydration

Based on laboratory and clinical TLS criteria (modified from Cairo and Bishop 2004), the following measures for TLS should be also followed

Laboratory tumor lysis syndrome

Defined as two or more of the following values within three days before or in the days following initiation of a treatment cycle:

- Uric acid ≥ 8 mg/dL or 25% increase from baseline
- Potassium ≥ 6 mEq/L or 25% increase from baseline
- Phosphorus or ≥ 4.5 mg/dL or 25% increase from baseline
- Calcium ≤ 7 mg/dL or 25% decrease from baseline

Regimen:

- If none or one of the laboratory values above is abnormal, continue to manage with allopurinol or a non-allopurinol alternative (e.g. febuxostat) and oral fluids. If uric acid remains elevated, consider IV fluids, rasburicase, and hospital monitoring.
- Laboratory TLS should be managed with IV fluids, laboratory blood tests every 6 to 8 hours and inpatient care. Cardiac monitoring and rasburicase should be considered if uric acid remain elevated.

Clinical tumor lysis syndrome

Defined as the presence of laboratory TLS and ≥ 1 of the following criteria that cannot be explained by other causes:

- Serum creatinine ≥ 1.5 times the upper limit of the age-adjusted normal range
- Symptomatic hypocalcemia
- Cardiac arrhythmia

Regimen: Clinical TLS should be managed with IV fluids, laboratory blood tests every 6 to 8 hours, cardiac monitoring, rasburicase/allopurinol/febuxostat and inpatient care (consider ICU). Subjects who have been treated for TLS with favorable outcome (defined as return to within 10% of baseline value or within limit of normal of relevant laboratory parameters) may re-start study treatment upon discussion between the sponsor and the investigator.

6.6.1 Treatment compliance

Study medication will be dispensed and/or administered at the site/clinic under the supervision of the investigator and/or study personnel during the study, including the extension treatment phase. This information should be captured in the source document and the eCRF at each visit. All study treatment administered must be recorded in the Drug Accountability Log.

For any study medication administered at home (such as ruxolitinib, siremadlin and rineterkib), the investigator must promote compliance by instructing the subject to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. A Patient Diary is available for use to support patient documentation of oral treatment compliance for those study medications administered at home. Patient Diary is no longer applicable in the extension treatment phase post amended protocol version 09 implementation. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts (if applicable) and information provided by the subject. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects as detailed in pharmacokinetics section, see Section 8.5.2.

6.6.2 Emergency breaking of assigned treatment code

Not applicable

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described in the investigational and control drugs Section 6.1.1.

A unique medication number is printed on the study medication label. This is not applicable for the local supply of ruxolitinib in USA.

Investigator staff will identify the study medication kits to dispense to the subject by contacting the IRT and obtaining the medication number(s). This is not applicable for the local supply of ruxolitinib in USA. The study medication has a 2-part label (base plus tear-off label). Immediately before dispensing the medication kit to the subject, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of investigational drug directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of investigational drug from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 2-months' supply. In this case, regular phone

calls or virtual contacts (every 4 weeks or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, drug accountability, investigation of any adverse events, ensuring the participant continues to benefit from treatment and discussion of the participant´s health status until the participant can resume visits at the study site.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure (IB). Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the subject except for the medication number (medication number not applicable for the local supply of ruxolitinib in USA).

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.1.2 Handling of additional treatment

Not applicable

6.7.2 Instruction for prescribing and taking study treatment

All kits of study treatment will be assigned by the IRT and will be recorded in the IRT system. This is not applicable for the local supply of ruxolitinib in USA.

6.7.2.1 Ruxolitinib

Ruxolitinib will be administered orally (PO) at 5-25 mg twice a day (BID) every day in a 28-day treatment cycle with or without food at the stable dose at the time of study entry. The subject should take the tablets at approximately the same time each day, with a glass of water. If the subject forgets to take a dose, then he/she should take ruxolitinib within 3 hours after the missed dose. If more than 3 hours have passed, then that missed dose should be omitted and the

patient should continue treatment with the next scheduled dose. Any missed study medication should be reported to the Investigator at the next study visit.

If vomiting occurs during the course of treatment, subjects should not take ruxolitinib again before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted in the adverse events section of the eCRF.

On the days that PK samples are obtained the subject should take the ruxolitinib tablets during the clinic visit after the pre-dose PK samples and prior to post-dose PK samples, when instructed by the study staff.

6.7.2.2 Siremadlin

Siremadlin (HDM201) capsules will be administered orally (PO) once daily (QD) on day 1 to 5 of every 28-day cycle at the indicated dose level (10 mg, 20 mg, 30 mg or 40 mg) on an empty stomach at least 1 hour before or 2 hours after a meal. The subject should take the capsules at approximately the same time each day of dosing, with a glass of water, swallowing whole without chewing the capsules, preferably with the morning dose of ruxolitinib. On days when siremadlin and ruxolitinib are administered at the same time, the dose of ruxolitinib should be taken in the fasted state together with siremadlin. If the subject is assigned to a siremadlin dose level where multiple capsules are to be taken, the capsules should be taken consecutively, within as short an interval as possible. If the subject forgets to take his/her daily dose, then he/she should restart the dose on the next scheduled dosing day without compensating for missed doses.

Subjects should be instructed not to make up missed doses. A missed dose is defined when the full dose is not taken within 8 hours after the approximate time of the usually daily dosing. That day's dose should be omitted and the subject should continue treatment with the next scheduled dose. Any missed study medication should be reported to the Investigator at the next study visit. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted in the adverse events section of the eCRF.

On the days that PK samples are obtained the subject should take the siremadlin and ruxolitinib tablets during the clinic visit after the pre-dose PK samples and prior to post-dose PK samples, when instructed by the study staff. The exact time for dose administration and breakfast (if applicable) intake must be recorded in the source documents and eCRF. In addition, on the days of full PK sampling, if a subject vomits within the first 4 hours after dose administration on that day, then the exact time of the first episode of vomiting should be recorded on the CRF and the dose should not be re-administered.

6.7.2.3 Crizanlizumab

Crizanlizumab (SEG101) will be administered at 5 mg/kg Q4W on Day 1 of every 28-day cycle with an additional loading dose administered at Cycle 1 Day 15 via IV infusion over 30 minutes (up to 2 hours, if clinically indicated) as described in the pharmacy manual starting approximately within the next hour after ruxolitinib administration, if and when administered. There should be a period of at least 1 hour after the infusion whereby the subject requires close observation.

6.7.2.4 Sabatolimab

Sabatolimab (MBG453) will be administered at 800 mg dose level Q4W on Day 1 of every 28-day cycle via IV infusion over 30 minutes (up to 2 hours, if clinically indicated) as described in the pharmacy manual starting approximately within the next hour after ruxolitinib administration, if and when administered. There should be a period of at least 1 hour after the infusion whereby the subject requires close observation.

6.7.2.5 Rineterkib

Rineterkib (LTT462) capsules will be administered orally (PO) once daily (QD) every day in a 28-day treatment cycle at the indicated dose level (100 mg, 200 mg or 300 mg) on an empty stomach at least 1 hour before or 2 hours after a meal. The subject should take the capsules at approximately the same time each day of dosing with a glass of water, swallowing whole without chewing the capsules, preferably with the morning dose of ruxolitinib. When rineterkib and ruxolitinib are administered at the same time, the dose of ruxolitinib should be taken in the fasted state together with rineterkib. If the subject is assigned to a rineterkib dose level where multiple capsules are to be taken, the capsules should be taken consecutively, within as short an interval as possible. If the subject forgets to take his/her daily dose, then he/she should restart the dose on the next scheduled dosing day without compensating for missed doses.

Subjects should be instructed not to make up missed doses. A missed dose is defined when the full dose is not taken within 8 hours after the approximate time of the usually daily dosing. That day's dose should be omitted and the subject should continue treatment with the next scheduled dose. Any missed study medication should be reported to the Investigator at the next study visit. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted in the adverse events section of the eCRF.

On the days that PK samples are obtained the subject should take the rineterkib capsules and ruxolitinib tablets during the clinic visit after the pre-dose PK samples and prior to post-dose PK samples, when instructed by the study staff. The exact time for dose administration and breakfast (if applicable) intake must be recorded in the source documents and eCRF. In addition, on the days of full PK sampling, if a subject vomits within the first 4 hours after dose administration on that day, then the exact time of the first episode of vomiting should be recorded on the CRF and the dose should not be re-administered.

6.7.2.6 NIS793

NIS793 will be administered at 2100 mg dose level Q3W on Day 1 of every 21-day cycle via IV infusion over at least 30-60 minutes as described in the pharmacy manual starting approximately within the next hour after ruxolitinib administration, if and when administered. The subject should be observed closely for a period of at least 2 hour after the infusion.

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents. In addition to the informed consent obtained before the screening procedures, subjects must be re-consented prior to entering the extension treatment phase.

Novartis will provide to investigators in a separate document a proposed ICF that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB) of each investigational drug. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

Male subjects must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

[redacted]

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

Subjects might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

As per Section 4.6, during a Public Health Emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, the Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Heath Authority. Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial subject and person obtaining informed consent, etc.).

8 Visit schedule and assessments

The assessment schedules in Table 8-2 and Table 8-4 for Part 1 of the study (Dose escalation and safety run-in) and Table 8-3 and Table 8-5 for Part 2 (Selection) and Part 3 (Expansion) of the study list all of the assessments and indicates with an "X" or "S" when they are to be performed. The assessment schedule used is dependent upon which study treatment combination the subject is assigned to. All data obtained from these assessments must be supported in the subject's source documentation, however an "S" on the assessment schedule indicates that the data can remain in the source documentation and will not be collected in the database. No CRF will be used as a source document. Additional assessments may be performed as clinically indicated.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final End of Treatment (EOT) visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

Study treatment will begin on Cycle 1 Day 1 (C1D1) with the first administration of the assigned study treatment, depending on the arm into which the subject has been allocated (Part 1) or randomized (Parts 2 and 3). C1D1 should occur on the same day as the allocation/randomization to study treatment, however if this is not logistically possible, it should not be more than 3 days after allocation/randomization in IRT. Each treatment cycle is 21 days for all treatment arms containing NIS793 or 28 days for all other treatment arms. It is recommended that a 28-day gap between Cycle (X) Day 1 and Cycle (X+1) Day 1 is maintained in ruxolitinib + siremadlin combination arm. The duration between cycles should not be shortened to < 28 days due to potential for additive hematotoxicity and adequate time for bone marrow recovery between cycles.

All study visits, assessments and study treatment administration are to be scheduled according to the appropriate number of calendar days from the day of first study treatment administration on C1D1 (whenever possible as per the allowable visit window specified in Table 8-1 below). If one of the investigational drugs is interrupted or permanently discontinued, at any time during the study, all study visits and safety assessments should continue according to the appropriate number of calendar days from C1D1 as per the schedule of assessments, and efficacy assessments must continue as per the scheduled number of weeks from C1D1 as described in

Table 8-2 (Part 1) and Table 8-3 (Parts 2 and 3) for treatment arms with 28-day cycles (all treatment arms not containing NIS793 except the monotherapy arm in Part 3 if ruxolitinib + NIS793 is chosen for Part 3), and Table 8-4 (Part 1) and Table 8-5 (Parts 2 and 3) for treatment arms containing NIS793.

Subjects will be treated for a planned duration of 8 cycles for arms with NIS793 or 6 cycles for all other arms in Part 1 (24 weeks), or for a planned duration of 16 cycles for NIS793 or 12 cycles for all other arms in Parts 2 and 3 (48 weeks).

In the context of enrollment halt, ongoing subjects from Part 1 who are benefitting from study treatment may continue to receive study treatment in the core treatment phase of Part 1 and be followed as per the schedule of assessments, as long as subjects derive benefit until the amended protocol version 08 is implemented. From the time of implementation of the amended protocol version 08, subjects who have received the combination treatment in the core treatment phase of Part 1 and benefitting from the allocated combination treatment may be eligible to continue on the same combination treatment in the extension treatment phase. These subjects will perform an End of Treatment visit for the core treatment phase to enter in the extension phase. The EOT (core treatment phase) visit is treated as Cycle 1 Day 1 of extension treatment phase and should occur on the same day, once the current cycle is completed i.e. on day 1 of next planned cycle to maintain treatment regimen.

The assessments schedule for Part 1 core and extension treatment phase are outlined in Table 8-2. Extension treatment phase is not applicable for the ruxolitinib+NIS793 arm (Table 8-4) as no subject was ongoing at time of the amended protocol version 08.

Subjects may be discontinued from treatment earlier due to unacceptable toxicity, disease progression or treatment is discontinued at the discretion of the investigator or the subject. Following treatment discontinuation, an EOT core visit will be performed for all subjects, after which safety follow-up visits are to be scheduled for subjects not entering the extension treatment phase.

For those subjects who enter the extension treatment phase and complete or discontinue earlier the extension treatment phase for any reason, an EOT extension visit will be performed for all subjects and after which safety follow-up visits are to be scheduled according to the appropriate number of calendar days after the last dose of study drug treatment administered depending on the investigational drug (refer to Section 9.2).

In addition, subjects in Part 2 and Part 3 will have a survival follow-up call every 3 months until the end of the study (Section 9.2). (Not applicable from amended protocol version 08).

Every effort must be made to follow the schedule of assessments within the windows outlined in the protocol.

Study visits with scheduled PK sampling should be scheduled in the morning so that a pre-dose PK blood sample can be collected.

The preferred sequence for assessments during study visits is ECG collection first, followed by vital signs, and blood sampling.

For Japan only, subjects enrolled in the crizanlizumab arm of Part 1 (Arm 2) are required to be hospitalized in the first 7 days of study treatment.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowed by local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

Table 8-1 Allowable visit windows

Visit name	Assessments	Window allowed
Screening	MRI/CT scan of abdomen (all parts)	within 8 weeks prior to first dose of study treatment
	Cardiac imaging (MUGA or echocardiogram or cardiac MRI) and ophthalmologic exams (Part1 only)	≤ 28 days before C1D1
	Bone marrow biopsy (part 2 and 3)	within 8 weeks prior to first dose of study treatment
	All other assessments	≤ 28 days before C1D1
C1D1 (Core Phase)	IRT dispensing call	-3 days
	Cardiac imaging (MUGA or echocardiogram or cardiac MRI) and ophthalmologic exams (Part 2 and Part 3)	-3 days
	All other visit assessments and administration of study drugs	NA
Day 1 visit of all subsequent cycles (Core and extension)	Cardiac imaging and ophthalmologic exams	-7 days
	All other visit assessments and administration of study drugs	± 3 days
During Treatment and Safety Follow-up periods	PK sampling	Refer to PK sample tables in Section 8.5.2
EOT Core Phase for subjects not entering in extension; EOT extension	All assessments	+ 7 days after last dose of study treatment (except for MRI/CT scan or bone marrow biopsy if completed in the past 12 weeks)
EOT core for subjects entering in extension and C1 D1 (extension)	All assessments	± 3 days (EOT core and C1D1 extension visits must be performed on the same day)
30-, 90-, and 105-day Safety Follow-up visit	All assessments	+ 7 days
150-day Safety Follow-up visit	All assessments	+ 14 days
Survival follow-up	All assessments	± 14 days

Table 8-2 Assessment Schedule, Part 1 (for all arms with 28-day cycles)

Period	**Screening**	**Core Treatment[1]**																								
Cycle		**Cycle 1**							**Cycle 2**					**Cycle 3**					**Cycle 4**			**Cycle 5**		
Days	**-28 to -1**	**1**	**2**	**5**	**6**	**8**	**15**	**16**	**1**	**2**	**5**	**6**	**15**	**1**	**2**	**5**	**8**	**15**	**1**	**2**	**5**	**1**	**2**	**5**
Informed consent	X																							
IRT screening call	X																							
Inclusion/exclusion criteria	X																							
IRT eligibility checklist and allocation call		X																						
Demography	X																							
Medical history	X																							
Disease diagnosis	X																							
Prior ruxolitinib therapy	X																							
Prior anti-neoplastic therapy	X																							
Prior/concomitant medications	X	X (at every clinic visit)																						
Non-drug therapies and procedures	X	X (at every clinic visit)																						
Transfusion record (PRBC and platelets)	X	X (at every clinic visit)																						
Physical examination	S	S							S					S					S			S		
ECOG performance status	X	X							X					X					X			X		
Height	X																							
Weight	X	X					X[2]		X					X					X			X		
Vital signs	X	X (at every clinic visit)																						
Spleen length measurement by palpation	X	X					X		X				X	X				X	X			X		
Laboratory assessments	-																							
Hematology	X	X					X		X				X	X				X	X			X		
Chemistry	X	X							X					X					X			X		
Additional chemistry for siremadlin safety monitoring[3]			X	X	X					X	X	X			X	X				X	X		X	X

Period	**Screening**	**Core Treatment[1]**																										
Cycle		**Cycle 1**							**Cycle 2**					**Cycle 3**					**Cycle 4**			**Cycle 5**		
Days	**-28 to -1**	**1**	**2**	**5**	**6**	**8**	**15**	**16**	**1**	**2**	**5**	**6**	**15**	**1**	**2**	**5**	**8**	**15**	**1**	**2**	**5**	**1**	**2**	**5**
Coagulation	X	X (as clinically indicated)																						
Urinalysis	X	X (as clinically indicated)																						
Thyroid function	X	X (as clinically indicated)																						
Pregnancy test - serum	S																							
Pregnancy test - urine or serum		S							S					S					S			S		
Hepatitis test	X[5]	X (as clinically indicated)																						
HIV screen	S[4]																							
Serology exam		X[6]	X (as clinically indicated)																					
Cytokines		X[7]	X (anytime if suspected cytokine release syndrome, immediately after the AE, and one week after the AE)																					
Safety	-																							
Adverse events	X	X (at every clinic visit)																						
ECG[8]	X	X		X[8]			X[8]		X[8]		X[8]			X[8]					X[8]			X[8]		
Cardiac imaging (MUGA scan or ECHO)		X[19]												X[19]										
Ophthalmologic assessments[19]	X[19]								X[19]					X[19]					X[19]			X[19]		
ePROs	-																							
MFSAF v4.0	X	X							X					X					X			X		
EORTC QLQ-C30	X	X							X					X					X			X		
[redacted]																								
TFQ (optional)		X																	X					
Imaging	-																							
MRI/CT of abdomen	X[9]																							
[redacted]																								

Period	**Screening**	**Core Treatment[1]**																										
Cycle		**Cycle 1**							**Cycle 2**					**Cycle 3**					**Cycle 4**			**Cycle 5**		
Days	**-28 to -1**	**1**	**2**	**5**	**6**	**8**	**15**	**16**	**1**	**2**	**5**	**6**	**15**	**1**	**2**	**5**	**8**	**15**	**1**	**2**	**5**	**1**	**2**	**5**
[redacted]																								
Disease progression assessment (Section 8.3.2.5)		X (at every clinic visit)																						
Confirmation of clinical benefit assessment (Section 8.3.3)																								
Study Drug Administration	-																							
IRT drug dispensation call							X2		X					X					X			X		
Ruxolitinib			X (BID - twice a day)																					
Siremadlin		X (Day 1-5)							X (Day 1-5)					X (Day 1-5)					X (Day 1-5)			X (Day 1-5)		
Crizanlizumab infusion		X					X		X					X					X			X		
Sabatolimab infusion		X							X					X					X			X		
Rineterkib		X (QD – once a day)																						
PK sampling	-																							
Ruxolitinib[10]		X	X	X[10]	X[10]		X		X	X[10]	X[10]	X[10]	X	X			X[10]		X	X		X[10]	X		X[10]
Siremadlin		X	X	X	X				X	X	X	X			X	X				X	X		X	X
Crizanlizumab		X	X			X	X		X					X	X		X	X	X			X		
Sabatolimab		X	X			X	X		X					X	X		X	X	X			X		
Blood sample for sTIM-3 (sabatolimab)		X	X			X	X		X					X	X		X	X	X			X		
Rineterkib		X	X				X	X	X					X					X			X		
Immunogenicity	-																							
Crizanlizumab		X							X					X					X			X		

Period	**Screening**	**Core Treatment[1]**																								
Cycle		**Cycle 1**							**Cycle 2**					**Cycle 3**					**Cycle 4**			**Cycle 5**		
Days	**-28 to -1**	**1**	**2**	**5**	**6**	**8**	**15**	**16**	**1**	**2**	**5**	**6**	**15**	**1**	**2**	**5**	**8**	**15**	**1**	**2**	**5**	**1**	**2**	**5**
Sabatolimab		X							X					X					X			X		
Anti-neoplastic therapy after discontinuation																								
IRT discontinuation call																								
Disposition[11]	X																							

Period	**Core Treatment[1]**				**End of Treatment (Core)[22]**	**Extension Treatment**		**End of Treatment (Extension)**	**Safety Follow-up[12]**		
Cycle	**Cycle 6**			**Cycle 7 and subsequent cycles***		**Cycle 1[22]**	**Cycle 2 and subsequent cycles**				
Days	**1**	**2**	**5**	**1**		**1**	**1**		**30 Days** (All)	**90 & 150 Days** (sabatolimab)	**105 Days** (Crizanlizumab)
Informed consent						X					
IRT screening call											
Inclusion/exclusion criteria						X					
IRT eligibility checklist and allocation call						X					
Demography											
Medical history											
Disease diagnosis											
Prior ruxolitinib therapy											
Prior anti-neoplastic therapy											
Prior/concomitant medications	X (at every clinic visit)				X	X	X	X	X	X	X

Period	**Core Treatment[1]**				**End of Treatment (Core)[22]**	**Extension Treatment**		**End of Treatment (Extension)**	**Safety Follow-up[12]**		
Cycle	**Cycle 6**			**Cycle 7 and subsequent cycles***		**Cycle 1[22]**	**Cycle 2 and subsequent cycles**				
Days	**1**	**2**	**5**	**1**		**1**	**1**		**30 Days** (All)	**90 & 150 Days** (sabatolimab)	**105 Days** (Crizanlizumab)
Non-drug therapies and procedures	X (at every clinic visit)				X	X	X	X	X	X	X
Transfusion record (PRBC and platelets)	X (at every clinic visit)				X	X[22]	X	X	X	X	X
Physical examination	S			S	S	S	S	S	S	S	S
ECOG performance status	X			X	X	X[22]	X	X			
Height											
Weight	X			X	X	X[22]	X	X			
Vital signs	X (at every clinic visit)				X	X[22]	X (at every clinic visit)	X	X	X	X
Spleen length measurement by palpation	X			X	X	X[22]	X	X			
Laboratory assessments	-										
Hematology	X			X	X	X[22]	X	X	X	X	X
Chemistry	X			X	X	X[22]	X	X	X	X	X
Additional chemistry for siremadlin safety monitoring[3]		X	X								
Coagulation	X (as clinically indicated)					X (as clinically indicated)					
Urinalysis	X (as clinically indicated)				X	X[22]		X			
Thyroid function	X (as clinically indicated)				X	X[22]		X			
Pregnancy test - serum					S			S	S	S	S

Period	**Core Treatment[1]**				**End of Treatment (Core)[22]**	**Extension Treatment**		**End of Treatment (Extension)**	**Safety Follow-up[12]**		
Cycle	**Cycle 6**			**Cycle 7 and subsequent cycles***		**Cycle 1[22]**	**Cycle 2 and subsequent cycles**				
Days	**1**	**2**	**5**	**1**		**1**	**1**		**30 Days** (All)	**90 & 150 Days** (sabatolimab)	**105 Days** (Crizanlizumab)
Pregnancy test - urine or serum	S			S		S	S				
Hepatitis test	X (as clinically indicated)				X		X (as clinically indicated)	X			
HIV screen											
Serology exam	X (as clinically indicated)					X (as clinically indicated)	X (as clinically indicated)				
Cytokines	X (anytime if suspected cytokine release syndrome, immediately after the AE, and one week after the AE)					X (anytime if suspected cytokine release syndrome, immediately after the AE, and one week after the AE)	X (anytime if suspected cytokine release syndrome, immediately after the AE, and one week after the AE)				
Safety	-										
Adverse events	X (at every clinic visit)				X	X	X	X	X	X	X
ECG[8]	X[8]			X[8]	X	X[22]	X (as clinically indicated)	X			
Cardiac imaging (MUGA or ECHO)					X[20]			X[20]			
Ophthalmologic assessments[19]	X[19]			X[19]	X[19]	X[22]	X[19]	X[19]			
ePROs	-										
MFSAF v4.0	X			X	X						
EORTC QLQ-C30	X			X	X						

Period	**Core Treatment[1]**				**End of Treatment (Core)[22]**	**Extension Treatment**		**End of Treatment (Extension)**	**Safety Follow-up[12]**		
Cycle	**Cycle 6**			**Cycle 7 and subsequent cycles***		**Cycle 1[22]**	**Cycle 2 and subsequent cycles**				
Days	**1**	**2**	**5**	**1**		**1**	**1**		**30 Days** (All)	**90 & 150 Days** (sabatolimab)	**105 Days** (Crizanlizumab)
[redacted]											
TFQ (optional)					X						
Imaging									-		
MRI/CT of abdomen				X[17]	X[13]	X[22]	X (as clinically indicated)	X[13]			
[redacted]											
Disease progression assessment (Section 8.3.2.5)	X (at every clinic visit)						X (at every clinic visit)				

Period	**Core Treatment[1]**				**End of Treatment (Core)[22]**	**Extension Treatment**		**End of Treatment (Extension)**	**Safety Follow-up[12]**		
Cycle	**Cycle 6**			**Cycle 7 and subsequent cycles***		**Cycle 1[22]**	**Cycle 2 and subsequent cycles**				
Days	**1**	**2**	**5**	**1**		**1**	**1**		**30 Days** (All)	**90 & 150 Days** (sabatolimab)	**105 Days** (Crizanlizumab)
Confirmation of clinical benefit assessment (Section 8.3.4)							X				
Study Drug Administration	-										
IRT drug dispensation call	X			X		X	X				
Ruxolitinib	X (BID - twice a day)					X	X				
Siremadlin	X (Day 1-5)			X (Day 1-5)		X (Day 1-5)	X (Day 1-5)				
Crizanlizumab infusion	X			X							
Sabatolimab infusion	X			X							
Rineterkib	X (QD – once a day)					X	X				
PK sampling	-										
Ruxolitinib[10]	X		X[10]								
Siremadlin		X	X								
Crizanlizumab	X			X[18]	X						X
Sabatolimab	X			X[18]	X					X[14]	
Blood sample for sTIM-3 (sabatolimab)	X			X[18]	X						
Rineterkib	X										
Immunogenicity	-										
Crizanlizumab	X			X[18]	X						X
Sabatolimab	X			X[18]	X					X[14]	

Period	**Core Treatment[1]**				**End of Treatment (Core)[22]**	**Extension Treatment**		**End of Treatment (Extension)**	**Safety Follow-up[12]**		
Cycle	**Cycle 6**			**Cycle 7 and subsequent cycles***		**Cycle 1[22]**	**Cycle 2 and subsequent cycles**				
Days	**1**	**2**	**5**	**1**		**1**	**1**		**30 Days** (All)	**90 & 150 Days** (sabatolimab)	**105 Days** (Crizanlizumab)
Anti-neoplastic therapy after discontinuation									X	X	X
IRT discontinuation call					X			X			
Disposition[11]					X			X			

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
* Only for subjects for which the investigator has confirmed continued clinical benefit after the first 6 planned cycles.
[1] Actual clinic visit days will depend on the treatment arm for PK, PD [redacted] collection: For all subjects = Day 1 & 2 of Cycle 1, Day 1 of all subsequent cycles, and Day 15 of Cycles 1, 2 & 3; For subjects on ruxolitinib + siremadlin = also Days 2 & 5 for any Cycle, and Day 6 of Cycle 1 & 2; For subjects on ruxolitinib + crizanlizumab and ruxolitinib + sabatolimab = also Day 8 of Cycle 1 & 3
[redacted]
[3] Additional chemistry only for subjects on ruxolitinib + siremadlin = phosphorus, calcium, uric acid, potassium, and creatinine
[4] As per country and local regulations
[5] Subjects that have a positive test for hepatitis should be re-tested pre-dose at the beginning of every cycle or as clinically indicated to monitor for hepatitis reactivation
[6] Only for subjects on the ruxolitinib + sabatolimab arm. Sample to be collected pre-dose.
[7] Only for subjects on the ruxolitinib + crizanlizumab and ruxolitinib + sabatolimab arms. Sample to be collected pre-dose.
[8] All subjects at screening, predose C1D1, and EOT. Also only for subjects on ruxolitinib + siremadlin = predose at C1D1, C1D5, C2D1, C2D5 and at 4h post-dose (Cmax) of C2D5, then pre-dose on Day 1 of Cycles 3-6 and then only if clinically relevant after Cycle 6. For subjects on ruxolitinib + rineterkib = predose at C1D1, predose and at 2h post-dose at C1D15, then pre-dose on Day 1 of Cycles 2-6 and then only if clinically relevant after Cycle 6.
[9] Previously completed scans can be considered for baseline if obtained within 8 weeks prior to first dose
[10] Refer to PK log tables for specific PK sampling depending on the combination treatment
[11] Subject disposition to be recorded in the eCRF
[12] Safety follow-up visits as follows: +30 days after last dose of all investigational drugs for all subjects; also +90 days and +150 days post last dose of sabatolimab for subjects on ruxolitinib + sabatolimab; and also +105 days post last dose of crizanlizumab for subjects on ruxolitinib + crizanlizumab
[13] If not performed in the past 12 weeks
[14] Only collected at the 90-day safety follow-up visit (not at the 150-day safety follow-up visit)
[redacted]
[16] Every 3 cycles after C6D1 until study treatment discontinuation (C9D1, C12D1 etc.) for subjects on ruxolitinib + crizanlizumab treatment
[17] At the end of every 6 cycles (± 7 days) for all subjects

Period	Core Treatment[1]				End of Treatment (Core)[22]	Extension Treatment		End of Treatment (Extension)	Safety Follow-up[12]		
Cycle	Cycle 6			Cycle 7 and subsequent cycles*		Cycle 1[22]	Cycle 2 and subsequent cycles				
Days	1	2	5	1		1	1		30 Days (All)	90 & 150 Days (sabatolimab)	105 Days (Crizanlizumab)

[18] Every 3 cycles until study treatment discontinuation (C9D1, C12D1 etc.)
[19] Only for subjects on ruxolitinib + rineterkib treatment
[20] Only for subjects on ruxolitinib + rineterkib treatment and if not performed within the last 14 days
[21] Every 6 cycles after C1D1 until study treatment discontinuation (C7D1, C13D1 etc.) for subjects on ruxolitinib + sabatolimab treatment
[22] Assessments performed for Core End of Treatment visit are not to be repeated for Extension Cycle 1 Day 1 as these two visits should occur on the same day. Corresponding data will be recorded only once in the CRF under Core Phase EOT visit.

Table 8-3 Assessment Schedule, Part 2 & 3 (for all arms with 28-day cycles) (Not applicable)

Period	Screening	Treatment[1]																			
Cycle		Cycle 1						Cycle 2			Cycle 3					Cycle 4			Cycle 5		
Days	-28 to -1	1	2	5	6	8	15	1	5	6	1	2	5	8	15	1	2	5	1	2	5
Informed consent	X																				
IRT screening call	X																				
Inclusion/exclusion criteria	X																				
IRT eligibility checklist and randomization		X																			
Demography	X																				
Medical history	X																				
Disease diagnosis	X																				
Prior ruxolitinib therapy	X																				
Prior anti-neoplastic therapy	X																				
Prior/concomitant medications	X	X (at every clinic visit)																			
Non-drug therapies and procedures	X	X (at every clinic visit)																			

Period	**Screening**	**Treatment[1]**																			
Cycle		**Cycle 1**						**Cycle 2**			**Cycle 3**					**Cycle 4**			**Cycle 5**		
Days	**-28 to -1**	**1**	**2**	**5**	**6**	**8**	**15**	**1**	**5**	**6**	**1**	**2**	**5**	**8**	**15**	**1**	**2**	**5**	**1**	**2**	**5**
Transfusion record (PRBC and platelets)	X	X (at every clinic visit)																			
Physical examination	S	S						S			S					S			S		
ECOG performance status	X	X						X			X					X			X		
Height	X																				
Weight	X	X					X[2]	X			X					X			X		
Vital signs	X	X (at every clinic visit)																			
Spleen length measurement by palpation	X	X					X	X			X				X	X			X		
Laboratory assessments	-																				
Hematology	X	X					X	X			X				X	X			X		
Chemistry	X	X						X			X					X			X		
Additional chemistry for siremadlin safety monitoring[3]			X	X	X				X	X		X	X				X	X		X	X
Coagulation	X	X (as clinically indicated)																			
Urinalysis	X	X (as clinically indicated)																			
Thyroid function	X	X (as clinically indicated)																			
Cardiac markers (Troponin I, NTproBNP)	X[21]																				
Pregnancy test - serum	S																				
Pregnancy test - urine		S						S			S					S			S		
Hepatitis test	X[5]	X (as clinically indicated)																			
HIV screen	S[4]																				
Serology exam		X[6]		X (as clinically indicated)																	
Cytokines		X[7]		X (anytime if suspected cytokine release syndrome, immediately after the AE, and one week after the AE)																	
Safety	-																				
Adverse events	X		X (at every clinic visit)																		

Period	**Screening**	**Treatment[1]**																			
Cycle		**Cycle 1**						**Cycle 2**			**Cycle 3**					**Cycle 4**			**Cycle 5**		
Days	**-28 to -1**	**1**	**2**	**5**	**6**	**8**	**15**	**1**	**5**	**6**	**1**	**2**	**5**	**8**	**15**	**1**	**2**	**5**	**1**	**2**	**5**
ECG[8]	X	X						X[8]			X[8]					X[8]			X[8]		
Cardiac imaging (MUGA or ECHO)[19]		X[19]									X[19]										
Ophthalmologic assessments[19]		X[19]						X[19]			X[19]					X[19]			X[19]		
Imaging	-																				
MRI/CT of abdomen	X[9]																				
ePROs	-																				
MFSAF v4.0	X	X						X			X					X			X		
EORTC QLQ-C30	X	X						X			X					X			X		
[redacted]																					
TFQ (optional)		X																			
[redacted]																					
Disease progression assessment		X (at every clinic visit)																			
Study Drug Administration	-																				
IRT drug dispensation call							X[2]	X			X					X			X		
Ruxolitinib		X (BID - twice a day)																			
Siremadlin		X (Day 1-5)						X (Day 1-5)			X (Day 1-5)					X (Day 1-5)			X (Day 1-5)		

Period	**Screening**	**Treatment[1]**																			
Cycle		**Cycle 1**						**Cycle 2**			**Cycle 3**					**Cycle 4**			**Cycle 5**		
Days	**-28 to -1**	**1**	**2**	**5**	**6**	**8**	**15**	**1**	**5**	**6**	**1**	**2**	**5**	**8**	**15**	**1**	**2**	**5**	**1**	**2**	**5**
Crizanlizumab infusion		X					X	X			X					X			X		
Sabatolimab infusion		X						X			X					X			X		
Rineterkib		X (QD – once a day)																			
PK sampling		-																			
Ruxolitinib[10]		X	X[10]	X[10]	X[10]		X[10]	X[10]	X[10]	X[10]	X		X[10]		X[10]	X		X[10]	X		X[10]
Siremadlin		X	X	X	X				X[10]	X		X	X				X	X		X	X
Crizanlizumab		X	X			X	X	X			X	X		X	X	X			X		
Sabatolimab		X	X			X	X	X			X	X		X	X	X			X		
Blood sample for sTIM-3 (sabatolimab)[#]		X	X			X	X	X			X	X		X	X	X			X		
Rineterkib		X	X				X	X			X					X			X		
Immunogenicity		-																			
Crizanlizumab		X						X			X					X			X		
Sabatolimab		X						X			X					X			X		
IRT discontinuation call																					
Anti-neoplastic therapy after discontinuation																					
Survival status																					
Leukemic transformation																					
Disposition[11]	X																				

Period	**Treatment**				**End of Treatment**	**Safety Follow-up[12]**			**Survival Follow-up**
Cycle	**Cycle 6**			**Cycle 7 (and subsequent cycles)***					
Days	**1**	**2**	**5**	**1**	**EOT**	**+30 Days (All)**	**+90 & +150 Days (sabatolimab)**	**+105 Days (crizanlizumab)**	**Every 3 months (All)**
Informed consent									
IRT screening call									
Inclusion/exclusion criteria									
IRT eligibility checklist and randomization									
Demography									
Medical history									
Disease diagnosis									
Prior ruxolitinib therapy									
Prior anti-neoplastic therapy									
Prior/concomitant medications	X (at every clinic visit)			X	X	X	X	X	
Non-drug therapies and procedures	X (at every clinic visit)			X	X	X	X	X	
Transfusion record (PRBC and platelets)	X (at every clinic visit)			X	X	X	X	X	
Physical examination	S			S	S	S	S	S	
ECOG performance status	X			X	X				
Height									
Weight	X			X	X				
Vital signs	X (at every clinic visit)			X	X	X	X		
Spleen length measurement by palpation	X			X	X				

Period	**Treatment**				**End of Treatment**	**Safety Follow-up[12]**			**Survival Follow-up**
Cycle	**Cycle 6**			**Cycle 7 (and subsequent cycles)***					
Days	**1**	**2**	**5**	**1**	**EOT**	**+30 Days (All)**	**+90 & +150 Days (sabatolimab)**	**+105 Days (crizanlizumab)**	**Every 3 months (All)**
Laboratory assessments	-								
Hematology	X			X	X	X	X	X	
Chemistry	X			X	X	X	X	X	
Additional chemistry for Siremadlin safety monitoring[3]		X	X						
Coagulation	X (as clinically indicated)								
Urinalysis	X (as clinically indicated)								
Thyroid function	X (as clinically indicated)				X				
Cardiac markers (Troponin I, NTproBNP)									
Pregnancy test - serum					S	S	S	S	
Pregnancy test - urine	S			S					
Hepatitis test	X (as clinically indicated)				X				
HIV screen									
Serology exam	X (as clinically indicated)				X				
Cytokines	X (anytime if suspected cytokine release syndrome, immediately after the AE, and one week after the AE)								
Safety									
Adverse events	X (at every clinic visit)			X	X	X	X	X	
ECG[8]	X[8]		X[8]	X[8]	X				
Cardiac imaging (MUGA or ECHO)[19]					X[20]				

Period	**Treatment**				**End of Treatment**	**Safety Follow-up[12]**			**Survival Follow-up**
Cycle	**Cycle 6**			**Cycle 7 (and subsequent cycles)***					
Days	**1**	**2**	**5**	**1**	**EOT**	**+30 Days (All)**	**+90 & +150 Days (sabatolimab)**	**+105 Days (crizanlizumab)**	**Every 3 months (All)**
Ophthalmologic assessments[19]	X[19]			X[19]	X[19]				
Imaging									
MRI/CT of abdomen				X[13]	X[14]				
ePROs									
MFSAF v4.0	X			X	X				
EORTC QLQ-C30	X			X	X				
[redacted]									
TFQ (optional)				X[23]	X				
[redacted]									
Disease progression assessment	X (at every clinic visit)								
Study Drug Administration									
IRT drug dispensation call	X			X					
Ruxolitinib	X (BID - twice a day)								
Siremadlin	X (Day 1-5)			X (Day 1-5)					
Crizanlizumab infusion	X			X					

Period	**Treatment**				**End of Treatment**	**Safety Follow-up[12]**			**Survival Follow-up**
Cycle	**Cycle 6**			**Cycle 7 (and subsequent cycles)***					
Days	**1**	**2**	**5**	**1**	**EOT**	**+30 Days (All)**	**+90 & +150 Days (sabatolimab)**	**+105 Days (crizanlizumab)**	**Every 3 months (All)**
Sabatolimab infusion	X			X					
Rineterkib	X (QD – once a day)								
PK sampling									
Ruxolitinib[10]	X		X[10]						
Siremadlin		X	X						
Crizanlizumab	X[15]				X			X	
Sabatolimab	X[15]				X		X[16]		
Blood sample for sTIM-3 (sabatolimab)#	X[15]				X				
Rineterkib	X								
Immunogenicity									
Crizanlizumab	X[15]				X			X	
Sabatolimab	X[15]				X		X[16]		
IRT discontinuation call					X				
Anti-neoplastic therapy after discontinuation						X	X	X	X
Survival status									X
Leukemic transformation									X
Disposition[11]					X				

X Assessment to be recorded in the clinical database or received electronically from a vendor

S Assessment to be recorded in the source documentation only

* Investigator will need to confirm continued clinical benefit for the subjects to continue beyond the first 12 planned cycles.

1 Actual clinic visit days will depend on the treatment arm for PK, PD [redacted] collection: For all subjects = Day 1 & 2 of Cycle 1, Day 1 of all subsequent cycles, and Day 15 of Cycles 1, 2 & 3; For subjects on ruxolitinib + siremadlin = also Days 2 & 5 for any Cycle, and Day 6 of Cycle 1 & 2; For subjects on ruxolitinib + crizanlizumab and ruxolitinib + sabatolimab = also Day 8 of Cycle 1 & 3

[redacted]

3 Additional chemistry for ruxolitinib + siremadlin subjects only (or siremadlin monotherapy arm in Part 3) = phosphorus, calcium, uric acid, potassium, and creatinine

Period	Treatment				End of Treatment	Safety Follow-up[12]			Survival Follow-up
Cycle	Cycle 6			Cycle 7 (and subsequent cycles)*					
Days	1	2	5	1	EOT	+30 Days (All)	+90 & +150 Days (sabatolimab)	+105 Days (crizanlizumab)	Every 3 months (All)

4 If required per As per country and local regulations

5 Subjects that have a positive test for hepatitis should be re-tested pre-dose at the beginning of every cycle or as clinically indicated to monitor for hepatitis reactivation

[redacted]

7 Only for subjects on the ruxolitinib + crizanlizumab and ruxolitinib + sabatolimab arms (or crizanlizumab or sabatolimab monotherapy arms in Part 3, as applicable), sample to be collected pre-dose.

8 All subjects at screening, predose C1D1, and EOT in Part 2 and 3. For ruxolitinib + siremadlin subjects only, as follows: Part 2 = also predose on Day 1 of cycles 2-6, and 4h postdose (Cmax) on C6D5, and then only if clinically relevant after Cycle 6; Part 3 = also predose on Day 1 of cycles 2, 4 & 6, and 4h postdose (Cmax) on C6D5, and then only if clinically relevant after Cycle 6. For subjects on ruxolitinib + rineterkib only, as follows: Part 2 = also pre-dose on Day 1 of Cycles 2-6 and then only if clinically relevant after Cycle 6, Part 3 = also pre-dose on Day 1 of Cycles 2, 4 & 6 and then only if clinically relevant after Cycle 6. Please see Section 8.4.2 for the list of requirements.

9 Previously completed MRI/CT scans and bone marrow biopsies can be considered for baseline if obtained within 8 weeks prior to first dose of study treatment.

10 Refer to PK log tables for specific PK sampling depending on the combination treatment

11 Subject disposition to be recorded in the eCRF

12 Safety follow-up visits as follows: +30 days after last dose of all investigational drugs for all subjects; also +90 days and +150 days post last dose of sabatolimab for subjects on ruxolitinib + sabatolimab (or sabatolimab monotherapy in Part 3); and also +105 days post last dose of crizanlizumab for subjects on ruxolitinib + crizanlizumab (or crizanlizumab monotherapy in Part 3)

13 At the end of every 6 cycles (± 7 days) for all subjects.

14 If not performed in the past 12 weeks

15 C6D1 then every 3 cycles until study treatment discontinuation (ie C9D1, C12D1 etc.)

16 Only collected at the 90-day safety follow-up visit (not at the 150-day visit)

[redacted]

18 C6D1 then every 3 cycles until study treatment discontinuation (C9D1, C12D1 etc.) for subjects on ruxolitinib + crizanlizumab treatment

19 Only for subjects on ruxolitinib + rineterkib treatment

20 Only for subjects on ruxolitinib + rineterkib treatment and if not performed within the last 14 days

21 Only when NIS793 is open for enrollment in Part 2 or 3.

22 Every 6 cycles after C1D1 until study treatment discontinuation (C7D1, C13D1 etc.) for subjects on ruxolitinib + sabatolimab treatment

[redacted]

Table 8-4 Assessment Schedule, Part 1 Ruxolitinib + NIS793 arm (21-day cycles)

Period	**Screening**	**Core Treatment**																	
Cycle		**Cycle 1**						**Cycle 2**		**Cycle 3**						**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycle 7**
Days	**-28 to -1**	**1**	**2**	**4**	**8**	**11**	**15**	**1**	**15**	**1**	**2**	**4**	**8**	**11**	**15**	**1**	**1**	**1**	**1**
Informed consent	X																		
IRT screening call	X																		
Inclusion/exclusion criteria	X																		
IRT eligibility checklist and allocation call		X																	
Demography	X																		
Medical history	X																		
Disease diagnosis	X																		
Prior ruxolitinib therapy	X																		
Prior anti-neoplastic therapy	X																		
Prior/concomitant medications	X	X (at every clinic visit)																	
Non-drug therapies and procedures	X	X (at every clinic visit)																	
Transfusion record (PRBC and platelets)	X	X (at every clinic visit)																	
Physical examination	S	S						S		S						S	S	S	S
ECOG performance status	X	X						X		X						X	X	X	X
Height	X																		
Weight	X	X						X		X						X	X	X	X
Vital signs	X	X (at every clinic visit)																	
Spleen length measurement by palpation	X	X					X	X	X	X					X	X	X	X	X
Laboratory assessments	-																		
Hematology	X	X					X	X	X	X					X	X	X	X	X
Chemistry	X	X						X		X						X	X	X	X

Period	**Screening**	**Core Treatment**																	
Cycle		**Cycle 1**						**Cycle 2**		**Cycle 3**						**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycle 7**
Days	**-28 to -1**	**1**	**2**	**4**	**8**	**11**	**15**	**1**	**15**	**1**	**2**	**4**	**8**	**11**	**15**	**1**	**1**	**1**	**1**
Coagulation	X	X (as clinically indicated)																	
Urinalysis	X	X						X		X						X	X	X	X
Thyroid function	X	X (as clinically indicated)																	
Cardiac markers (Troponin I,NTproBNP)	X									X								X	
Pregnancy test - serum	S																		
Pregnancy test - urine or serum		S						S		S						S	S	S	S
Hepatitis test	X[1]	X (as clinically indicated)																	
HIV screen	S[2]																		
Serology exam		X[3]	X (as clinically indicated)																
Cytokines		X[3]	X (anytime if suspected cytokine release syndrome, immediately after the AE, and one week after the AE)																
Safety	-																		
Adverse events	X	X (at every clinic visit)																	
ECG	X	X						X		X						X	X	X	X
ePROs	-																		
MFSAF v4.0	X	X						X		X						X	X	X	X
EORTC QLQ-C30	X	X						X		X						X	X	X	X
[redacted]																			
TFQ (optional)		X														X			
Imaging	-																		
MRI/CT of abdomen	X[4]																		
Cardiac Imaging: Echocardiogram (or if not available, Cardiac MRI)	X																		
[redacted]																			

Period	**Screening**	**Core Treatment**																	
Cycle		**Cycle 1**						**Cycle 2**		**Cycle 3**						**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycle 7**
Days	**-28 to -1**	**1**	**2**	**4**	**8**	**11**	**15**	**1**	**15**	**1**	**2**	**4**	**8**	**11**	**15**	**1**	**1**	**1**	**1**
[redacted]																			
Disease progression assessment		X (at every clinic visit)																	
Study Drug Administration	-																		
IRT drug dispensation call		X						X		X						X	X	X	X
Ruxolitinib		X (BID - twice a day)																	
NIS793		X						X		X						X	X	X	X
PK sampling	-																		
Ruxolitinib[5]		X						X		X					X	X	X	X	X
NIS793		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Immunogenicity	-																		
NIS793		X						X		X						X	X	X	X
Anti-neoplastic therapy after discontinuation																			
IRT discontinuation call																			
Disposition[6]	X																		

Period	**Core Treatment**		**End of Treatment (Core)**	**Safety Follow-up**	
Cycle	**Cycle 8**	**Cycle 9 and subsequent cycles***			
Days	**1**	**1**	**EOT**	**30 Days**	**90 Days**
Informed consent					
IRT screening call					
Inclusion/exclusion criteria					
IRT eligibility checklist and allocation call					
Demography					
Medical history					
Disease diagnosis					
Prior ruxolitinib therapy					
Prior anti-neoplastic therapy					
Prior/concomitant medications	X (at every clinic visit)		X	X	X
Non-drug therapies and procedures	X (at every clinic visit)		X	X	X
Transfusion record (PRBC and platelets)	X (at every clinic visit)		X	X	X
Physical examination	S	S	S	S	S
ECOG performance status	X	X	X		
Height					
Weight	X	X	X		
Vital signs	X (at every clinic visit)		X	X	X
Spleen length measurement by palpation	X	X	X		
Laboratory assessments					
Hematology	X	X	X	X	X
Chemistry	X	X	X	X	X
Coagulation	X (as clinically indicated)				
Urinalysis	X	X	X		
Thyroid function	X (as clinically indicated)		X		
Cardiac markers (Troponin I, NTproBNP)		X^{10}		X^{10}	
Pregnancy test - serum			S	S	S

Period	**Core Treatment**		**End of Treatment (Core)**	**Safety Follow-up**	
Cycle	**Cycle 8**	**Cycle 9 and subsequent cycles***			
Days	**1**	**1**	**EOT**	**30 Days**	**90 Days**
Pregnancy test - urine or serum	S	S			
Hepatitis test	X (as clinically indicated)		X		
HIV screen					
Serology exam	X (as clinically indicated)				
Cytokines	X (anytime if suspected cytokine release syndrome, immediately after the AE, and one week after the AE)				
Safety					
Adverse events	X (at every clinic visit)		X	X	X
ECG	X	X	X		
ePROs					
MFSAF v4.0	X	X	X		
EORTC QLQ-C30	X	X	X		
[redacted]					
TFQ (optional)			X		
Imaging					
MRI/CT of abdomen		X[7]	X[8]		
Cardiac Imaging Echocardiogram (or if not available, Cardiac MRI)		X[11]		X	
[redacted]					

Period	**Core Treatment**		**End of Treatment (Core)**	**Safety Follow-up**	
Cycle	**Cycle 8**	**Cycle 9 and subsequent cycles***			
Days	**1**	**1**	**EOT**	**30 Days**	**90 Days**
Disease progression assessment	X (at every clinic visit)				
Study Drug Administration					
IRT drug dispensation call	X	X			
Ruxolitinib	X (BID - twice a day)				
NIS793	X	X			
PK sampling					
Ruxolitinib[5]	X				
NIS793	X	X[9]	X	X	X
Immunogenicity					
NIS793	X	X[9]	X	X	X
Anti-neoplastic therapy after discontinuation				X	X
IRT discontinuation call			X		
Disposition[6]			X		

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only

* Only for subjects for which the investigator has confirmed continued clinical benefit after the first 6 planned cycles.

1 Subjects that have a positive test for hepatitis should be re-tested pre-dose at the beginning of every cycle or as clinically indicated to monitor for hepatitis reactivation
2 As per country and local regulations

3 Sample to be collected pre-dose.
4 Previously completed scans can be considered for baseline if obtained within 8 weeks prior to first dose
5 Refer to PK log tables for specific PK sampling depending on the combination treatment
6 Subject disposition to be recorded in the eCRF
7 At the end of every 8 cycles (± 7 days)

8 If not performed in the past 12 weeks

9 Every 4 cycles after C8D1 until study treatment discontinuation, pre-dose at the beginning of the next cycle (C12D1, C16D1 etc.)

10 Every 3 cycles after C3D1 until study treatment discontinuation, pre-dose at the beginning of the cycle (C6D1, C9D1...) also as clinically indicated.

11 If a patient continued beyond planned duration of 8 cycles, pre-dose at the beginning of the cycle at C9D1 (at 24 weeks) also as clinically indicated and/or if cardiac enzyme increase ≥ 2x ULN (if normal at screening), or ≥ 2x baseline (if baseline value was elevated).

Table 8-5 Assessment Schedule, Part 2 & 3 Ruxolitinib + NIS793 or NIS793 monotherapy arm (21-day cycles) (Not applicable)

Period	**Screening**	**Treatment**													
Cycle		**Cycle 1**				**Cycle 2**		**Cycle 3**				**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycle 7**
Days	**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**15**	**1**	**2**	**8**	**15**	**1**	**1**	**1**	**1**
Informed consent	X														
IRT screening call	X														
Inclusion/exclusion criteria	X														
IRT eligibility checklist and allocation call		X													
Demography	X														
Medical history	X														
Disease diagnosis	X														
Prior ruxolitinib therapy	X														
Prior anti-neoplastic therapy	X														
Prior/concomitant medications	X	X (at every clinic visit)													
Non-drug therapies and procedures	X	X (at every clinic visit)													
Transfusion record (PRBC and platelets)	X	X (at every clinic visit)													
Physical examination	S	S				S		S				S	S	S	S
ECOG performance status	X	X				X		X				X	X	X	X
Height	X														
Weight	X	X				X		X				X	X	X	X
Vital signs	X	X (at every clinic visit)													
Spleen length measurement by palpation	X	X			X	X	X	X			X	X	X	X	X
Laboratory assessments	-														
Hematology	X	X			X	X	X	X			X	X	X	X	X
Chemistry	X	X				X		X				X	X	X	X

Period	**Screening**	**Treatment**													
Cycle		**Cycle 1**				**Cycle 2**		**Cycle 3**				**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycle 7**
Days	**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**15**	**1**	**2**	**8**	**15**	**1**	**1**	**1**	**1**
Coagulation	X	X (as clinically indicated)													
Urinalysis	X	X				X		X				X	X	X	X
Thyroid function	X	X (as clinically indicated)													
Cardiac markers (Troponin I, NTproBNP)	X							X						X	
Pregnancy test - serum	S														
Pregnancy test - urine or serum		S				S		S				S	S	S	S
Hepatitis test	X[1]	X (as clinically indicated)													
HIV screen	S[2]														
Serology exam		X[3]	X (as clinically indicated)												
Cytokines		X[3]	X (anytime if suspected cytokine release syndrome, immediately after the AE, and one week after the AE)												
Safety	-														
Adverse events	X	X (at every clinic visit)													
ECG	X	X				X		X				X	X	X	X
ePROs	-														
MFSAF v4.0	X	X				X		X				X	X	X	X
EORTC QLQ-C30	X	X				X		X				X	X	X	X
[redacted]															
TFQ (optional)		X													
Imaging	-														
MRI/CT of abdomen	X[4]														
Cardiac Imaging: Echocardiogram (or if not available, Cardiac MRI)		X													
[redacted]															

Period	**Screening**	**Treatment**													
Cycle		**Cycle 1**				**Cycle 2**		**Cycle 3**				**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycle 7**
Days	**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**15**	**1**	**2**	**8**	**15**	**1**	**1**	**1**	**1**
[redacted]															
Disease progression assessment		X (at every clinic visit)													
Study Drug Administration	-														
IRT drug dispensation call		X				X		X				X	X	X	X
Ruxolitinib		X (BID - twice a day)													
NIS793		X				X		X				X	X	X	X
PK sampling	-														
Ruxolitinib[5]		X				X		X			X	X	X	X	X
NIS793		X	X	X	X	X		X	X	X	X	X	X	X	X
Immunogenicity	-														
NIS793		X				X		X				X	X	X	X
Anti-neoplastic therapy after discontinuation															
IRT discontinuation call															
Survival status															
Leukemic transformation															
Disposition[6]	X														

Period	**Treatment**		**End of Treatment**	**Safety Follow-up**		**Survival Follow-up**
Cycle	**Cycle 8**	**Cycle 9 and subsequent cycles***				
Days	**1**	**1**	**EOT**	**30 Days**	**90 Days**	**Every 3 months**
Informed consent						
IRT screening call						
Inclusion/exclusion criteria						
IRT eligibility checklist and allocation call						
Demography						
Medical history						
Disease diagnosis						
Prior ruxolitinib therapy						
Prior anti-neoplastic therapy						
Prior/concomitant medications	X (at every clinic visit)		X	X	X	
Non-drug therapies and procedures	X (at every clinic visit)		X	X	X	
Transfusion record (PRBC and platelets)	X (at every clinic visit)		X	X	X	
Physical examination	S	S	S	S	S	
ECOG performance status	X	X	X			
Height						
Weight	X	X	X			
Vital signs	X (at every clinic visit)		X	X	X	
Spleen length measurement by palpation	X	X	X			
Laboratory assessments	-					
Hematology	X	X	X	X	X	
Chemistry	X	X	X	X	X	
Coagulation	X (as clinically indicated)					
Urinalysis	X	X	X			

Period	**Treatment**		**End of Treatment**	**Safety Follow-up**		**Survival Follow-up**
Cycle	**Cycle 8**	**Cycle 9 and subsequent cycles***				
Days	**1**	**1**	**EOT**	**30 Days**	**90 Days**	**Every 3 months**
Thyroid function	X (as clinically indicated)		X			
Cardiac markers (Troponin I, NTproBNP)		X[10]		X		
Pregnancy test - serum			S	S	S	
Pregnancy test - urine or serum	S	S				
Hepatitis test	X (as clinically indicated)		X			
HIV screen						
Serology exam	X (as clinically indicated)					
Cytokines	X (anytime if suspected cytokine release syndrome, immediately after the AE, and one week after the AE)					
Safety	-					
Adverse events	X (at every clinic visit)		X	X	X	
ECG	X	X	X			
ePROs	-					
MFSAF v4.0	X	X	X			
EORTC QLQ-C30	X	X	X			
[redacted]						
TFQ (optional)	X		X			
Imaging	-					
MRI/CT of abdomen		X[7]	X[8]			
Cardiac imaging: Echocardiogram (or if not available, Cardiac MRI)		X[11]		X		
[redacted]						

Period	**Treatment**		**End of Treatment**	**Safety Follow-up**		**Survival Follow-up**
Cycle	**Cycle 8**	**Cycle 9 and subsequent cycles***				
Days	**1**	**1**	**EOT**	**30 Days**	**90 Days**	**Every 3 months**
[redacted]						
Disease progression						
Disease progression assessment	X (at every clinic visit)					
Study Drug Administration	-					
IRT drug dispensation call	X	X				
Ruxolitinib	X (BID - twice a day)					
NIS793	X	X				
PK sampling	-					
Ruxolitinib[6]	X					
NIS793	X	X[9]	X	X	X	
Immunogenicity	-					
NIS793	X	X[9]	X	X	X	
Anti-neoplastic therapy after discontinuation				X	X	X
IRT discontinuation call			X			
Survival status						X
Leukemia transformation						X
Disposition[11]			X			

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only

* Only for subjects for which the investigator has confirmed continued clinical benefit after the first 6 planned cycles.

[1] Subjects that have a positive test for hepatitis should be re-tested pre-dose at the beginning of every cycle or as clinically indicated to monitor for hepatitis reactivation
[2]As per country and local regulations

Period	Treatment		End of Treatment	Safety Follow-up		Survival Follow-up
Cycle	Cycle 8	Cycle 9 and subsequent cycles*				
Days	1	1	EOT	30 Days	90 Days	Every 3 months

[3] Sample to be collected pre-dose.
[4] Previously completed MRI/CT scans and bone marrow biopsies can be considered for baseline if obtained within 8 weeks prior to first dose of study treatment. For re-screened subjects.
[5] Refer to PK log tables for specific PK sampling depending on the combination treatment
[6] Subject disposition to be recorded in the eCRF
[7] At the end of every 8 cycles (± 7 days)
[8] If not performed in the past 12 weeks
[9] Every 4 cycles after C8D1 until study treatment discontinuation, pre-dose at the beginning of the next cycle (C12D1, C16D1 etc.)
[10] Every 3 cycles after C3D1 until study treatment discontinuation, pre-dose at the beginning of the cycle (C6D1, C9D1...) also as clinically indicated.
[11] At C9D1 (24 weeks) and also as clinically indicated and/or if cardiac enzyme increase ≥ 2x ULN (if normal at screening), or ≥ 2x baseline (if baseline value was elevated).

[redacted]

8.1 Screening

The screening period begins once written informed consent is provided and ends after 28 days or when subject is allocated (Part 1) /randomized (Parts 2 and 3) to study treatment, whichever comes first.

Screening assessments to confirm eligibility into the study, as described in Table 8-2 and Table 8-3, Table 8-4 and Table 8-5 should be performed within 1 to 28 days prior to the first dose of study treatment, unless otherwise specified in Table 8-1.

A serum pregnancy test, where applicable, must be confirmed negative prior to the first dose of study treatment.

A subject who has a laboratory test result(s) that does not satisfy the entrance criteria may have the test(s) repeated once, prior to randomization. These test(s) may be repeated as soon as the investigator believes the re-test result(s) is/are likely to be within the acceptable range to satisfy the entrance criteria, but should be completed within approximately 3 weeks of the original screening visit date. In this case, the subject will not be required to sign another ICF, and the original subject ID number assigned by the investigator will be used. In the event that the laboratory test(s) cannot be performed within 3 weeks of the original screening visit, or the re-test(s) do not meet the entrance criteria, or other eligibility criteria have changed and are not met anymore, the subject is considered a screen failure.

A new ICF will need to be signed if the investigator chooses to re-screen the subject after a subject has screen failed. A new subject ID number will be used. All required screening activities must be performed when the subject is re-screened for participation in the study to satisfy eligibility requirements. An individual subject may only be re-screened once for the study. Once the number of subjects screened and enrolled is likely to ensure target enrollment, Novartis may close the study to further screening. In this case, the subjects who screen failed will not be permitted to re-screen.

8.1.1 Eligibility screening

Following registering in the IRT for screening, subject eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

8.1.2 Information to be collected on screening failures

Part 1 subjects who sign an ICF and subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be entered on the applicable CRF. The demographic information, informed consent, disease diagnosis, prior ruxolitinib treatment, Inclusion/Exclusion pages and study disposition must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event during the screening phase (see SAE Section 10.1.2 for reporting details).

Part 1 subjects who sign an informed consent and are considered eligible but fail to be started on treatment for any reason will be considered an early terminator. The reason for early termination should be captured on the appropriate disposition CRF.

Part 2 and Part 3 subjects who sign the study ICF but are subsequently found to be ineligible prior to randomization will be considered a screen failure. The demographic information, informed consent, and Inclusion/Exclusion and study disposition pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event during the screening phase (see SAE Section 10.1.2 for reporting details). If the subject fails to be randomized, the IRT must be notified within 2 days of the screen fail that the subject was not randomized.

Part 2 and Part 3 subjects who are randomized and fail to start study treatment for any reason will be considered an early terminator. The reason for early termination should be recorded on the appropriate CRF.

8.2 Subject demographics/other baseline characteristics

The following data on subject characteristics will be collected at screening for all Parts of the study as listed in Table 8-2, Table 8-3, Table 8-4 and Table 8-5:

- Demographic information: age at consent, gender, ethnicity and race *(if permitted)*
- Participant race/ethnicity data are collected and analyzed to identify any difference in the safety and/or efficacy profile of the treatment due to these characteristics. In addition, the diversity of the study population should be taken into consideration to support subgroup analysis as required by some Health Authorities. Relevant medical history (including medical conditions present at time of ICF signature)
- Diagnosis of disease
- Prior ruxolitinib treatment (≥ 12 weeks and on a stable dose ≥ 4 weeks)
- All prior anti-neoplastic therapies (medications, surgeries, radiation)
- Prior and concomitant medications: All medications and significant non-drug therapies taken within 30 days prior to the first dose of study treatment must be recorded in the CRF. They will be updated on a continuous basis if there are any new changes to the medications.
- HIV history (If mandated per local requirements, a local HIV testing is to be done during screening)
- Transfusion record for PRBC and platelets

Subjects will have the following screening assessments performed before the start of study treatment in all Parts of the study as listed in Table 8-2, Table 8-3, Table 8-4 and Table 8-5:

- Physical examination
- Height
- Weight
- Vital signs

- Laboratory assessments - Hematology, chemistry, coagulation, urinalysis, thyroid function, Troponin I and NTproBNP for NIS793 patients in Part 1 and all patients in part 2 and 3 if NIS793 is open for enrollment.
- Hepatitis test
- HIV screen (if required per local regulations)
- Serum pregnancy test
- Spleen measurement by palpation
- Baseline MRI/CT (if not already performed within 8 weeks prior to first dose of study treatment)
- PRO questionnaires (MFSAF v4.0 and EORTC QLQ-C30)
- Bone marrow biopsy and aspirate for measuring bone marrow fibrosis changes (Parts 2 and 3)
- [redacted]
- ECOG performance status
- ECG
- Cardiac imaging as required based on the allocated study treatment.

8.3 Efficacy

As the enrollment was permanently halted, the only randomized subject in Part 2 has discontinued prior to this amendment, and Part 3 will not be initiated, therefore the descriptions of endpoints for Parts 2 and 3 are not applicable. Secondary efficacy endpoints for Part 1 are outlined in Table 2-1.

8.3.1 Response rate for the composite primary efficacy endpoint

The primary efficacy endpoint for Part 2 and Part 3 is the response rate (RR) of the composite of the following, assessed at the end of Cycle 8 (for treatment arms with NIS793) or Cycle 6 (for all other treatment arms) Section 12.4.1:

- Improvement in anemia of ≥ 1.5 g/dL, and
- No spleen volume progression, and
- No symptoms worsening

The composite criteria are defined as follows:

- Anemia improvement requires an increase of hemoglobin from baseline of at least 1.5 g/dL
- Spleen volume progression is defined as a spleen volume increase of 25% or more from baseline as determined by MRI/CT
- Symptoms worsening is defined as a total symptom score (TSS) increase of 10 or more from baseline assessed by MFSAF version 4.0

The following assessments will be utilized to determine the 3 components for the RR

8.3.1.1 Improvement in Anemia

Anemia improvement requires an increase of hemoglobin from baseline of at least 1.5 g/dL as measured at the end of Cycle 8 (arms with NIS793) or Cycle 6 (all other arms). The increase in hemoglobin should be confirmed at least 2 weeks later. Anemia improvement requires the absence of any PRBC transfusion in the 12 weeks prior to achieving an increase of 1.5 g/dL.

Laboratory Hb assessments (as outlined in Section 8.4.1) taken at the end of Cycle 8 (arms with NIS793) or Cycle 6 (all other arms) in comparison to C1D1 will be used to determine those subjects that achieved an improvement of ≥ 1.5 g/dL.

8.3.1.2 Spleen volume progression

Evaluation of spleen volume will be performed by Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) scan. MRI of the spleen (or CT if MRI is contraindicated) will be performed as regular assessment at screening, and at the end of Cycle 8 (arms with NIS793) or Cycle 6 (all other arms) in comparison to the screening assessment (baseline). Previously completed scans can be considered for baseline if obtained within 8 weeks prior to first dose of study treatment (C1D1).

Volumetric spleen size progression is defined as a spleen volume increase of at least 25% from baseline, as per IWG-MRT revised criteria (Tefferi et al 2013).

MRI will be performed with a body coil because the objective is to measure organ volume, not to find very small lesions. MRIs will be performed and assessed by local radiologists who will be instructed to provide a quantitative and a qualitative assessment of spleen volume (as enlarged, smaller, larger, etc.). The MRI will not determine spleen length below the costal margin, as there are no validated approaches for determining this measurement. The site radiologist will provide the read-out and the results from the local evaluations will be used for the endpoints analyses.

MRI is the preferred method for obtaining spleen volume data. However, CT scans may be performed at the visits where MRI would be conducted if the subject is not a candidate for MRI (because of the presence of metal clips in the body, or because of claustrophobia, for example), or if MRI is unavailable to the study site.

Generally, the same method (MRI or CT) should be consistently used for all visits for a given subject unless a new contraindication to the use of MRI (eg, pacemaker insertion) occurs.

Any imaging assessments already completed during the regular work-up of the subject within 8 weeks prior to start of study treatment, including before signing the main study ICF, can be considered as the baseline images for this study. Any imaging assessments obtained after allocation (Part 1)/randomization (Part 2 and Part 3) cannot be considered baseline images.

Imaging assessments during the study should be scheduled using the allocation/randomization date as the reference date and should be respected regardless of whether study treatment is temporarily withheld or unscheduled assessments performed.

Additional imaging assessments may be performed at any time during the study at the investigator's discretion to support the efficacy evaluations for a subject, as necessary. Clinical suspicion of disease progression at any time requires a physical examination and imaging

assessments to be performed promptly rather than waiting for the next scheduled imaging assessment.

8.3.1.3 Total symptom score (TSS) worsening

Symptom worsening occurs when the total symptom score (TSS) assessed by MFSAF v4.0 increases 10 or more scores from baseline (C1D1) at the end of Cycle 8 (arms with NIS793) or Cycle 6 (all other arms). Refer to Section 8.5.1 for a description of the MFSAF v4.0 PRO. The TSS absolute increase of 10 or more from baseline is considered as a clinical meaningful symptom worsening based on the COMFORT I trial data using a combination of distribution- and anchor- based approaches (Dueck et al 2017). An absolute score change, rather than a percentage change, is the criterion as the latter would either require not enough change in magnitude for a lower baseline or too much change in magnitude for a higher baseline.

8.3.2 Secondary efficacy endpoints

The following assessments will be performed for each treatment arm as secondary efficacy endpoints in Parts 2 and 3.

Changes in spleen size and volume and MFSAF v4.0 Total Symptoms Score will be assessed as secondary endpoints for Part 1 (core and/or extension) as outlined in Table 2-1:

- Hb measurement to assess proportion of subjects who achieved improvement in Hb level of ≥ 1.5 g/dL or ≥ 2.0 g/dL
- Evaluation of a change in spleen length by palpation and spleen volume by MRI/CT
- Changes in MFSAF v4.0 and EORTC QLQ-C30
- Estimation of time to PFS events
- Evaluation of the effect on bone marrow fibrosis

8.3.2.1 Proportion of subjects achieving improvement of Hb level (Not applicable)

The improvement in anemia based on an increase of hemoglobin from baseline of at least ≥ 1.5 g/dL or ≥ 2.0 g/dL is assessed at the end of Cycle 8 (for arms with NIS793) or Cycle 6 (all other arms) and at the end of Cycle 16 (arms with NIS793) or Cycle 12 (all other arms). The increase in hemoglobin should be confirmed at least 2 weeks later.

Anemia improvement requires the absence of any PRBC transfusion in the 12 weeks prior to achieving an increase of 1.5 g/dL or 2.0 g/dL.

Laboratory Hb assessments (as outlined in Section 8.4.1) taken at the end of Cycle 8 (for arms with NIS793) or Cycle 6 (all other arms) and at the end of Cycle 16 (arms with NIS793) or Cycle 12 (all other arms) will be compared to baseline (C1D1) to determine the proportion of those subjects that have achieved an improvement of ≥ 1.5 g/dL or ≥ 2.0 g/dL from baseline.

8.3.2.2 Changes in spleen length and spleen volume

Evaluation of spleen size changes for secondary endpoint will be assessed by performing manual palpation and MRI/CT imaging as outlined below.

Spleen length assessment by manual palpation

Spleen length measurements will be conducted by manual palpation at regular intervals during the study in order to evaluate changes in spleen length in each treatment arm. Manual palpation will be performed on days 1 and 15 of cycles 1 to 3, and day 1 of subsequent cycles, as noted in the schedule of assessments in Table 8-2 to Table 8-5.

The edge of the spleen shall be determined by palpation, and measured in centimeters (not fingerbreadths), from the lower costal margin (LCM) to the point of greatest splenic protrusion.

In case of spleen length increase that meets any of the criteria for progressive spleen size as described below are met, an MRI/CT scan will be conducted to confirm spleen size progression.

- Appearance of a new splenomegaly that is palpable at least 5cm below the LCM, or
- A ≥ 100% increase in palpable distance, below LCM, for baseline splenomegaly of 5-10 cm, or
- A 50% increase in palpable distance, below LCM, for baseline splenomegaly of > 10 cm, as per IWG-MRT revised criteria (Tefferi et al 2013).

In case any of the criteria for progressive spleen size as described above are met, MRI/CT scan will be conducted to confirm spleen size progression.

Spleen volume assessment by MRI or CT scan

Assessment of spleen volume by MRI (or CT if MRI is contraindicated) will be performed as described in Section 8.3.1.2 at screening (baseline), at the end of Cycle 8 (arms with NIS793) or Cycle 6 (all other arms), then every 8 cycles (arms with NIS793) or 6 cycles (all other arms), and at EOT (if not performed in the past 12 weeks) as noted in Table 8-6. Previously completed scans can be considered for baseline if obtained within 8 weeks prior to first dose of study treatment.

During the extension treatment phase, assessment of spleen volume by MRI or CT scan should be performed as needed by investigator to assess subject spleen response and clinical benefit of study treatment.

Table 8-6 MRI/CT Assessment Collection Plan

Procedure	Timepoints
Abdomen MRI or CT	• Screening/baseline (Day -28 to day-1) • At the end of every 8 cycles for arms with NIS793 or 6 cycles for all other arms (± 7 days) • EOT (if not performed in last 12 weeks) • Treatment extension phase – as needed by investigator • Unscheduled – at the discretion of investigator

8.3.2.3 Change in MFSAF v4.0 and EORTC QLQ-C30

The changes in symptoms of myelofibrosis in each treatment arm using MFSAF v4.0 and EORTC QLQ-C30 patient reported outcomes (PROs) from baseline will be evaluated. Refer to Section 8.5.1 for details of these PROs.

8.3.2.4 Progression Free Survival

Progression free survival endpoint is not applicable as Part 2 and 3 endpoints will not be pursued.

Progression free survival (PFS) is defined as the time from randomization until earliest time for one of the following progression events.

- Progressive splenomegaly as assessed by increasing spleen volume (by MRI/CT) of ≥ 25% from baseline
- Accelerated phase defined by an increase in circulating peripheral blood blast content of > 10% but < 20% confirmed after 2 weeks. The progression date will be the date of first increase in peripheral blood blast content of > 10%
- Deteriorating cytopenia (dCP) independent from treatment defined for all patients by platelet count < 35 x10^9/L or neutrophil count < 0.75 x 10^9/L that lasts for at least 4 weeks. The progression date will be the date of first decrease of platelets < 35 x10^9/L or neutrophils < 0.75 x 10^9/L confirmed after 4 weeks
- Leukemic transformation defined by an increase in peripheral blood blast content of ≥ 20% associated with an absolute blast count of ≥ 1x10^9/L that lasts for at least 2 weeks or a bone marrow blast count of ≥ 20%. The progression date will be the date of first increase in peripheral blood blast content of ≥ 20% associated with an absolute blast count of ≥ 1x10^9/L OR the date of the bone marrow blast count of ≥ 20% as per IWG-MRT revise criteria (Tefferi et al 2013).
- Death from any cause.

Progressive splenomegaly:

For the PFS assessment progressive splenomegaly is defined as an increased spleen volume from baseline of at least 25% as measured by MRI/CT.

The spleen length regular assessment done by palpation will be used to trigger splenomegaly progression.

In case of spleen length increase that meet any of the criteria for progressive spleen size as described below are met, MRI/CT will be conducted to confirm spleen size progression.

- Appearance of a new splenomegaly that is palpable at least 5cm below the LCM, or
- A ≥ 100% increase in palpable distance, below LCM, for baseline splenomegaly of 5-10 cm, or
- A 50% increase in palpable distance, below LCM, for baseline splenomegaly of > 10 cm

The progression date will be the date of MRI/CT assessment confirming spleen volume increase of at least 25% from baseline

For patients meeting the progressive disease criteria the Investigator must review according to the guidance below, and confirm the relevant criterion. The data should be entered in the appropriate CRF and IRT notified.

8.3.2.5 Disease progression

The progression events as defined in Section 8.3.2.4 bullets will be assessed as one of the criteria for leading to discontinuation of study treatment (Section 9.1.1).

Guidance for progressive disease criterion assessment is as follows:

- Earliest confirmed single disease progression criterion should be entered.
- If more than one criterion are confirmed on the same date, time or visit; progressive disease should be assessed using the single criterion based on the hierarchy below:
  1. Death
  2. Leukemic transformation
  3. Accelerated phase
  4. Progressive splenomegaly
  5. Deteriorating cytopenia

8.3.2.6 Change in bone marrow fibrosis and histomorphology (Not applicable)

In Part 2 and Part 3 of the study, bone marrow fibrosis will be measured in grades from samples obtained from subjects at screening and at the end of Cycle 8 (for arms with NIS793) or Cycle 6 (for all other arms), then every six cycles and at EOT per Table 8-7.

Table 8-7 Bone Marrow Assessment Collection Plan

Procedure	Timepoints
Bone marrow biopsy and aspirate	• Screening* • At the end of every 8 cycles for arms with NIS793 or at the end of every 6 cycles for all other arms (pre-dose at the beginning of the next cycle, e.g. C7D1 or C9D1 etc.) • EOT (if not performed in the last 12 weeks)
* Bone marrow biopsies collected within 8 weeks of C1D1 are acceptable for baseline assessment. Bone marrow aspirates should be collected at screening (within 28 days of C1D1), however for re-screened subjects, aspirates collected within 8 weeks of C1D1 are acceptable.	

Collection, processing and staining of bone marrow aspirations and paraffin embedded bone marrow core biopsy block samples for local analysis will be done in accordance with standard procedures at the investigative site. The bone marrow aspirate should be assessed at local investigative site by an experienced hematopathologist using his/her standard examination. Bone marrow fibrosis should be graded using the grading system as applied by European consensus according to "The 2016 revision to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia" (Arber et al 2016), as presented in Table 8-8.

Table 8-8 Grading of myelofibrosis

Myelofibrosis grading	
MF - 0	Scattered linear reticulin with no intersections (crossovers) corresponding to normal BM
MF - 1	Loose network of reticulin with many intersections, especially in perivascular areas
MF - 2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with focal bundles of thick fibers mostly consistent with collagen, and/or focal osteosclerosis*
MF - 3	Diffuse and dense increase in reticulin with extensive intersections and coarse bundles of thick fibers consistent with collagen, usually associated with osteosclerosis*
Note: Semiquantitative grading of BM fibrosis (MF) with minor modifications concerning collagen and osteosclerosis. Fiber density should be assessed only in hematopoietic areas. * In grades MF-2 or MF-3 an additional trichrome stain is recommended.	

Changes in bone marrow fibrosis of at least 1 grade will be assessed as a secondary endpoint in Part 2 and Part 3. The following assessments should be performed:

- Assessment of cellularity.
- 500-cell differential of aspirate, correlated, if possible, with data from appropriate marrow biopsy section. Percentage of pronormoblasts, blasts, normoblasts, myelocytes, metamyelocytes.
- Blast percentage, indicating what cellular types are being considered as blast equivalents, and the degree of maturation and dysplastic abnormalities within the neoplastic population should be described.
- Characterization of erythrocyte and megakaryocyte morphology.
- Characterization and gradation of fibrosis within hematopoietic cellular areas.
- Diagnostic interpretation with specific mention of (expected) absence of an infiltrative or granulomatous process.

Cytogenetic analysis should include karyotyping and any other tests for which an abnormality has been previously identified in that subject. Any other tests that are considered standard by the Investigator may also be performed.

8.3.3 Appropriateness of efficacy assessments

Not applicable

8.3.4 Extension treatment phase Efficacy Assessment

For subjects entering the extension treatment phase, the investigator is required to confirm that the subject continues to derive clinical benefit and may continue receiving study treatment at every visit during extension treatment phase. This includes an assessment of disease progression as per definition of disease progression in Section 8.3.2.5.

8.4 Safety and tolerability

Safety assessments are specified below in Table 8-9 and Table 8-10 and with the assessment schedule in Table 8-2, Table 8-3, Table 8-4 and Table 8-5 detailing when each assessment is to be performed during the study. These include a physical examination, vital signs, weight, laboratory assessments, ECOG performance status and ECGs, as well as the collection of AEs at every clinic visit. For details on AE collection and reporting, refer to Section 10.1

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 4 weeks or more frequently if needed) for safety monitoring and discussion of the subject´s health status until it is safe for the subject to visit the site again.

Additional safety monitoring for Tumor Lysis Syndrome (TLS)

TLS is a known risk for patients with hematological malignancies, and was observed in two subjects diagnosed with AML and administered siremadlin in study CHDM201X2101. Therefore, additional safety assessments will be collected for subjects on the ruxolitinib and

siremadlin arm in this study to monitor for signs and symptoms of TLS. In addition to the full chemistry panel collected as outlined in Table 8-2 and Table 8-3, phosphorus, calcium, uric acid, potassium, and creatinine will also be measured on Days 2, 5 and 6 of Cycle 1 and Cycle 2, and Days 2 and 5 for Cycles 3-6, and then only when clinically indicated. Refer to Section 6.6 for additional information.

Table 8-9 Safety & tolerability assessments & specifications

Assessment	Specification
Physical	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. A complete physical examination should be conducted at screening and baseline (pre-dose C1D1) for Parts 1, 2 and 3 of the study. If indicated, based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic examinations will be performed. A short physical examination will include the examination of general appearance along with vital signs. A short physical examination may be conducted in Part 1, 2 and 3 of the study starting from for all visits after baseline (C1D1) except where a complete physical examination is required when clinically indicated or based on symptoms. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes)
Performance status	ECOG Performance status scale will be used as described in Table 8-10.

Table 8-10 ECOG Performance Status

	ECOG 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 (e.g., light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

8.4.1 Laboratory evaluations

A local laboratory will be used for all planned laboratory assessments listed in Table 8-2, Table 8-3, Table 8-4 and Table 8-5, except cytokines and serology, which will be evaluated by a central laboratory. Refer to Table 8-11 for a summary of the parameters to be evaluated. The laboratory parameters must be performed as per the schedule in Table 8-2, Table 8-3, Table 8-4 and Table 8-5.

The laboratory assessments listed are for all subjects in the study except as follows. Serology examination for anti-drug antibodies (ADAs) will be evaluated pre-dose at Cycle 1 Day 1 and

then when clinically indicated for subjects on the ruxolitinib + sabatolimab combination treatment arm (and the sabatolimab monotherapy arm in Part 3, if applicable) and the ruxolitinib + NIS793 combination treatment arm (and the NIS793 monotherapy arm in Part 3, if applicable). This is based on potential AEs of immune-mediated etiology reported in sabatolimab monotherapy and combination studies and NIS793 combination studies, respectively. Cytokines will be evaluated pre-dose at Cycle 1 Day 1 and then when clinically indicated for suspected cytokine release syndrome for subjects on ruxolitinib + crizanlizumab combination treatment (and crizanlizumab monotherapy in Part 3, if applicable), for subjects on ruxolitinib + sabatolimab combination treatment (and sabatolimab monotherapy in Part 3, if applicable) and for subjects on ruxolitinib + NIS793 combination treatment (and NIS793 monotherapy in Part 3, if applicable).

There are no specific notable range criteria for this study; however, the local and central laboratory will flag laboratory values falling outside of the normal range on the local and central laboratory report (as applicable) as per local practice, and the Investigator will report any values considered clinically significant in the eCRF. Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate.

Sites will be requested to provide the local laboratory reference ranges and a copy of the laboratory certification to Novartis for all local laboratory results recorded in the eCRF.

Crizanlizumab laboratory test interference - automated platelet counts

Interference with automated platelet counts (i.e. unevaluable result) for SCD patients treated with crizanlizumab have been observed in clinical studies when blood samples are drawn in tubes containing ethylenediaminetetraacetic acid (EDTA) and analyzed by a central laboratory. Platelet clumping has been reported by the central lab in approximately half of the blood samples collected in EDTA-tubes. This observation led to an *ex vivo* study to assess the impact of time and anti-coagulant used (i.e. EDTA vs citrate) on the interference with automated platelet counts.

This observation led to an ex vivo study to assess the impact of time and anti-coagulant used (i.e. EDTA vs citrate) on the interference with automated platelet counts.

Blood was collected from healthy volunteer donors using either EDTA or citrate as anticoagulant. The results of this study indicated that crizanlizumab induced EDTA- and time-dependent platelet clumping ex vivo in serum anticoagulated with EDTA, resulting in an interference with the automated platelet count. This effect was not observed when using citrate tubes, or when EDTA-samples were analyzed within 4 hours post blood collection, and was enhanced when blood samples were primed with thrombin in order to pre-activate platelets, thereby increasing platelet surface P-selectin expression.

There is no evidence that crizanlizumab causes a reduction in circulating platelets or has a pro-aggregant effect *in vivo*. Recommendations that may mitigate this laboratory interference are:

1. Collect the sample for platelet count in a tube with citrate as anticoagulant
2. Analyze platelet count in a local lab as soon as possible. Based on in vitro data, platelet clumping was observed in some donor samples as early as 4 hours following the addition of crizanlizumab.

3. Review peripheral smear for platelet clumping and manual platelet estimation, if necessary.

Table 8-11 Clinical laboratory parameters collection plan

Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells differential - Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils (absolute value preferred, %s are acceptable), Circulating peripheral blasts
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus (inorganic phosphorus) , Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Total Bilirubin, Direct Bilirubin (only if Total Bilirubin is ≥ Grade 2), Indirect Bilirubin (only if Total Bilirubin is out of range), Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (fasting)
Urinalysis	Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) (unless local institution policies dictate otherwise) Microscopic Panel if clinically indicated (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells)
Coagulation	International normalized ratio [INR]), Activated partial thromboplastin time (APTT)
Thyroid function	T4 [free], TSH
Hepatitis markers	HBV-DNA, HBsAg, HBsAb, HBcAb, HCV RNA-PCR
HIV screen	If required per local regulations
Serology examination*	Anti-DNA antibodies (Abs), Anti-nuclear Abs, Anti-phospho lipid Abs, Anti-mitochondrial Abs, c-Reactive protein (CRP), Rheumatoid factor (RF)
Cytokines*	IFN-γ, IL-6, IL-1, TNF-α
Pregnancy Test	Serum or urine pregnancy test only for women of child-bearing potential depending on the timepoint (refer to 'Pregnancy and assessments of fertility' Section 8.4.5)
* To be performed by a central laboratory: Serology for all treatment combinations with sabatolimab or NIS793; Cytokines for all treatment combinations with crizanlizumab, sabatolimab or NIS793.	

8.4.2 Electrocardiogram (ECG)

Standard 12 lead ECGs are to be collected locally with ECG machines available at the site. ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling.

At baseline, a minimum of 3 sequential, individual ECGs should be recorded at least 5 minutes apart. The mean QTcF value will be calculated from the triplicate ECGs for each subject. The Fridericia QT correction formula (QTcF) should be used for clinical decisions. Refer to section Dose adjustments in the case of QTcF prolongation (Section 6.5.4.1).

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate. For any ECGs with subject safety concerns, two additional ECGs must be performed to confirm the safety finding. A monitoring or review process should be in place for clinically significant ECG findings throughout the study and especially at baseline before administration of study treatment. Clinically significant ECG findings at baseline must be discussed with the sponsor before administration of any study treatment. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page.

The ECG collection plan for ruxolitinib + siremadlin (or siremadlin monotherapy in Part 3) is noted in Table 8-12. Considering the potential cardiac risks (AV block, atrial fibrillation, QT prolongation) associated with siremadlin observed in phase I and II monotherapy and combination trials, cardiac risk is being monitored frequently. The ECG collection plan for subjects on ruxolitinib single agent, ruxolitinib + crizanlizumab (or crizanlizumab monotherapy in Part 3), ruxolitinib + sabatolimab (or sabatolimab monotherapy in Part 3 is less frequent and is listed in Table 8-13. Cardiac toxicity is a known risk for MAPK pathway inhibitors such as MEK inhibitors, therefore the cardiac risk will be more frequently monitored for subjects on ruxolitinib + rineterkib (or rineterkib monotherapy in Part 3) even though no drug related cardiac toxicity event has been reported so far in rineterkib studies (Janku et al 2020). The ECG collection plan for ruxolitinib + rineterkib (or rineterkib monotherapy in Part 3) is noted in Table 8-14. For NIS793, given the preclinical findings outlined in Section 1.1.2.6 of vascular inflammation, ECGs will be performed every cycle as noted in Table 8-15 .

As there is a potential food effect related to siremadlin, it is recommended a fixed food-drug schedule for all patients, preferably drug intake 2 hours after a meal, as this can affect the QTc findings by almost 10 msec.

Interpretation of the tracing must be made by a qualified physician and documented on the appropriate CRF. Each ECG tracing should be labeled with the study number, subject initials (where regulations permit), subject number, date, and kept in the source documents at the study site.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected in triplicate.

Table 8-12 ECG timepoints for ruxolitinib + siremadlin (or siremadlin monotherapy) treatment

Visit /Cycle	Timepoint for ruxolitinib + siremadlin			ECG Type
	Part 1	Part 2	Part 3	
Screening	Any time	Any time	Any time	Single
C1D1	Pre-dose	Pre-dose	Pre-dose	Triplicate
C1D5	Pre-dose	Not applicable	Not applicable	Single
C2D1	Pre-dose	Pre-dose	Pre-dose	Single
C2D5	Pre-dose	Not applicable	Not applicable	Single
	4h post dose after administration of siremadlin	Not applicable	Not applicable	Single
C3D1	Pre-dose	Pre-dose	Not applicable	Single
C4D1	Pre-dose	Pre-dose	Pre-dose	Single
C5D1	Pre-dose	Pre-dose	Not applicable	Single
C6D1	Pre-dose	Pre-dose	Pre-dose	Single
C6D5	Not applicable	4h post dose after administration of siremadlin	4h post dose after administration of siremadlin	Single
Subsequent cycles	Only if clinically relevant	Only if clinically relevant	Only if clinically relevant	Single

Visit /Cycle	Timepoint for ruxolitinib + siremadlin			ECG Type
	Part 1	Part 2	Part 3	
(Core and Extension phase)				
EOT (Core and Extension phase)	Any time	Any time	Any time	Single
Unscheduled	Any time	Any time	Any time	Triplicate

Table 8-13 ECG timepoints for ruxolitinib single agent, ruxolitinib + crizanlizumab (or crizanlizumab monotherapy), ruxolitinib + sabatolimab (or sabatolimab monotherapy)

Visit /Cycle	ECG Time-points	ECG Type
Screening	Any time	Single
C1D1	Pre-dose	Triplicate
EOT	Any time	Single
Unscheduled	Any time	Triplicate

Table 8-14 ECG timepoints for ruxolitinib + rineterkib treatment (or rineterkib monotherapy)

Visit /Cycle	Timepoint for ruxolitinib + rineterkib			ECG Type
	Part 1	Part 2	Part 3	
Screening	Any time	Any time	Any time	Single
C1D1	Pre-dose	Pre-dose	Pre-dose	Triplicate
C1D15	Pre-dose	Not applicable	Not applicable	Single
C1D15	2h post-dose after administration of rineterkib	Not applicable	Not applicable	Single
C2D1	Pre-dose	Pre-dose	Pre-dose	Single
C3D1	Pre-dose	Pre-dose	Not applicable	Single
C4D1	Pre-dose	Pre-dose	Pre-dose	Single
C5D1	Pre-dose	Pre-dose	Not applicable	Single
C6D1	Pre-dose	Pre-dose	Pre-dose	Single
Subsequent cycles (Core and Extension phase)	Only if clinically relevant	Only if clinically relevant	Only if clinically relevant	Single
EOT (Core and Extension phase)	Any time	Any time	Any time	Single
Unscheduled	Any time	Any time	Any time	Triplicate

Table 8-15 ECG timepoints for ruxolitinib + NIS793 treatment (or NIS793 monotherapy)

Visit /Cycle	ECG Time-points	ECG Type
Screening	Any time	Triplicate
C1D1	Pre-dose	Triplicate
C2D1 and all other cycles (Core phase)	Pre-dose	Triplicate

Visit /Cycle	ECG Time-points	ECG Type
EOT (Core phase)	Any time	Triplicate
Unscheduled	Any time	Triplicate

8.4.3 Cardiac markers

For patients to be enrolled to NIS793 arm cardiac specific markers Troponin I and NTproBNP will be performed at the following timepoints:

- at screening for all patients in part 1 and all patients in Part 2 and 3 if NIS793 is open for enrollment
- at C3D1 pre-dose, and at every third cycle thereafter, and as clinically indicated during treatment duration and at the 30-day safety follow-up visit after EOT for patients allocated to NIS793.
- patients with elevated cardiac enzymes ≥ 2xULN (if normal at screening), or ≥ 2x baseline (if baseline value was elevated) will have cardiac imaging (echocardiogram) performed

8.4.4 Cardiac imaging - MUGA scan or ECHO or cardiac MRI

Left ventricular ejection fraction (LVEF) decrease is a class effect of MEK inhibitors, therefore subjects treated with rineterkib will be closely monitored with a multigated acquisition (MUGA) scan or echocardiogram (ECHO).

Subjects allocated to arms containing rineterkib in Part 1 and subjects randomized to arms containing rineterkib in Part 2 and Part 3 (if applicable), will have a MUGA scan or ECHO to assess LVEF prior to dosing on C1D1 (i.e. within 28days from C1D1 for part 1, and within 3 days from C1D1 for part 2 and 3), at C3D1 and Core and Extension Treatment EOT, as outlined in Table 8-2 and Table 8-3 within the windows outlined in Table 8-1.

Additional assessments may be performed if clinically indicated. A MUGA scan or ECHO will be performed at EOT core and extension only if an assessment of LVEF has not been performed ≤ 14 days prior to EoT.

Cardiac imaging i.e. echocardiogram or cardiac MRI if echocardiogram is not available or otherwise indicated will also be performed prior to dosing at screening for Part 1 within ≤ 28 days before C1D1 and, for parts 2 and 3 at C1D1, to determine cardiac function and morphology at baseline for all patients receiving NIS793 in light of the preclinical findings outlined in Section 1.1.2.6.

Thereafter, the cardiac imaging will be performed for patients enrolled to NIS793 arm during the treatment period as described below:

- in Part 1: 30-day safety follow-up visit after core treatment EOT and at anytime as clinically indicated and/or if Troponin I is elevated > 2x ULN. If patients continue beyond planned duration of 8 cycles in part 1, then cardiac imaging should be done also at C9D1 as applicable.
- in Parts 2 and 3: at C9D1 and 30-day safety follow-up after EOT and at anytime as clinically indicated and/or if Troponin I is elevated > 2x ULN.

Cardiac imaging assessments for patients receiving NIS 793 are outlined in Table 8-4 and Table 8-5 and within the windows outlined in Table 8-1.

The same assessment method will be used throughout the study for each patient. When possible, the same cardiologist or radiologist should read and report the outcome to minimize the variability in results.

8.4.5 Ophthalmologic assessment

Since ocular AEs has been observed but resolved over time in other rineterkib studies (Janku et al 2020), subjects on ruxolitinib + rineterkib (or rineterkib monotherapy in Part 3) will be monitored for ocular toxicity at the beginning of each cycle and as clinically indicated.

A full ophthalmologic examination including slit lamp examination, visual acuity testing (preferably Snellen or Early Treatment Diabetic Retinopathy Study (ETDRS)), visual field testing, tonometry (Intra Ocular Pressure (IOP)), and indirect fundoscopy (with dilation) with attention to retinal abnormalities (especially signs of central serous retinopathy and RVO), should be performed by an ophthalmologist at screening for Part 1 subjects who are allocated to receive rineterkib and for subjects randomized to arms with rineterkib in Part 2 and Part 3, if applicable, prior to dosing on C1D1. Similar assessments will then be performed and the beginning of every cycle only for subjects in arms with rineterkib, as outlined in Table 8-2 and Table 8-3 within the windows outlined in Table 8-1.

Optical coherence tomography (OCT) will be performed at baseline prior to dosing on C1D1 together with the above ophthalmologic assessments, then as clinically indicated for subjects in arms with rineterkib.

For patients with clinical suspicion of retinal changes, additional assessments of fluorescein angiography and/or OCT should be performed upon the discretion of the treating physician. Any observed abnormalities and/or changes to Screening/baseline must be documented in the Adverse Events eCRF.

In addition to the assessments performed by the ophthalmologist, subjective ophthalmic examination will be done by the investigator during each physical examination to monitor potential eye toxicity only for subjects in arms with rineterkib. During this subjective ophthalmic evaluation, the investigator will check for any new sign of visual disturbance, ocular discomfort, or any new abnormal ocular appearance.

For patients with new ocular symptoms or findings that are considered clinically relevant by the investigator, an ophthalmologist should be consulted within 72 hours.

8.4.6 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have serum pregnancy testing at screening, the end of treatment and at the safety follow-up visits. Additional serum (preferred) or urine pregnancy testing will be performed at the beginning of every cycle.

Local pregnancy tests and associated results will not be collected on the CRF.

If subjects cannot visit the site to have serum pregnancy tests, urine pregnancy test kits may be used. Subjects can perform the urine pregnancy test at home and report the result to the site. It

is important that subjects are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the subject so that the site is informed and can verify the pregnancy test results (e.g. following Country specific measures).

Assessments of Fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female subject regardless of reported reproductive/menopausal status at screening/baseline.

8.4.7 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/subject population.

[redacted]

8.5.1 Clinical Outcome Assessments (COAs)

Collection of COAs will not apply to subjects entering the Part 1 extension treatment phase.

Patient reported outcomes (PRO)

Subjects with MF often experience significant symptoms that interfere with their quality of life (QoL) including fatigue, early satiety, pruritus, weight loss, weakness and night sweats. The effect of ruxolitinib combination treatment on subject symptoms and QoL will be measured using three PRO assessment tools: the MF Symptom Assessment Form version 4.0 (MFSAF v4.0); the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), and the [redacted]

The PRO questionnaires will be provided electronically (ePRO) to the subject at the clinic visit and collected according to the visit schedules outlined in Table 8-2, Table 8-3, Table 8-4 and Table 8-5 before any clinical assessments are conducted. The ePRO measures should be completed by the subject in the language most familiar to the subject. The subject should be given sufficient space and time to complete the ePRO measures. The ePRO measures should be completed in the same order at each visit to ensure the subject is answering them as consistently

as possible. The measures should be given in the following order: MFSAF v4.0, EORTC QLQ-C30, [redacted]

Subject's refusal to complete all or any part of an ePRO measure should be documented in the study data capture system and should not be captured as a protocol deviation. Handling of protocol deviations can be modified if needed per study protocol.

The site personnel should check the ePRO measures for completeness and ask the subject to complete any missing responses. The responses stored electronically on the database will be considered the source file.

Completed measures and any unsolicited comments written by the subject should be reviewed and assessed by the investigator for responses which may indicate potential AEs or SAEs before any clinical study examinations. This assessment should be documented in study source records. If AEs or SAEs are confirmed, study investigators should not encourage the subject to change responses reported in the completed questionnaires. Study investigators must follow reporting instructions outlined in Section 10 (e.g. reference "Adverse Events" section) of the study protocol.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, PROs may be collected remotely (e.g. web portal, telephone interviews) depending on local regulations, technical capabilities, and following any applicable training in the required process.

MFSAF v4.0

MFSAF v4.0 (Section 16.3 in Appendix 3) is a harmonized, consensus-based PRO questionnaire recently developed for use in MF trials by a PRO Consortium Working Goup (Gwaltney et al 2017), which focuses on the 7 core symptoms of MF: fatigue, night sweats, pruritus, abdominal discomfort, pain under the ribs on the left side, early satiety and bone pain.

Subjects record symptom severity at it worst for each of the 7 symptoms on an 11-point numeric rating scale, from 0 (absent) to 10 (worst imaginable). The Total Symptom Score (TSS) is calculated as the average of the observed individual item responses on the 0 to 10 scale multiplied by 7. The MFSAF v4.0 has two formats, 24-h recall and 7-day recall. The 7-day recall format will be used in this study.

MFSAF v4.0 will be collected at Screening, C1D1, Day 1 of all subsequent cycles of treatment, as well as the EOT visit, as shown in Table 8-2, Table 8-3, Table 8-4 and Table 8-5.

EORTC QLQ-C30

The EORTC QLQ-C30 PRO (Section 16.4 in Appendix 4) is one of the most widely used and validated instruments to measure health-related quality of life (QoL) in subjects with cancer (Aaronson et al 1993). The core questionnaire, the QLQ-C30 version 3.0, is the current standard. The EORTC QLQ-C30 includes 5 functional scales (physical, emotional, social, role, cognitive), eight symptom scales (fatigue, pain, nausea/vomiting, constipation, diarrhea, insomnia, dyspnea, and appetite loss), as well as global health/quality-of-life and financial impact. This instrument asks the subject to respond according to the past week recall period, with the exception of the first 5 questions that represent physical functioning and capture the subject's current status.

Raw scores are linearly converted to a 0–100 scale. For functional and global health status/QoL scales, higher scores indicate better QoL and level of functioning; for symptom scales, higher scores indicate greater level of symptoms or difficulties.

As indicated in Table 8-2, Table 8-3, Table 8-4 and Table 8-5, the EORTC QLQ-C30 will be collected at Screening, C1D1, Day 1 of all subsequent cycles of treatment, as well as the EOT visit.

[redacted]

Trial Feedback

This study is including an optional questionnaire, the 'Trial Feedback Questionnaire' (TFQ) for trial subjects to provide feedback on their clinical trial experience. Individual trial subject responses will not be reviewed by investigators. Responses may be used by the sponsor (Novartis) to understand where improvements can be made in the clinical trial process. This questionnaire does not ask question about the subject's disease, symptoms, treatment effect, or adverse events, and, therefore is not considered as trial data. The TFQ is not considered study data and will be received electronically outside of the clinical database.

8.5.2 Pharmacokinetics

Blood samples for Pharmacokinetic (PK), immunogenicity (IG) or pharmacodynamics (PD) will be obtained from all subjects who receive at least one dose of ruxolitinib, siremadlin, crizanlizumab, sabatolimab, rineterkib and NIS793. IG samples will also be collected to monitor appearance of anti-drug antibodies (ADAs) directed against crizanlizumab, sabatolimab and NIS793. The time points of blood collection for each respective investigational drug are outlined in Table 8-16 to Table 8-24 . As a result of the permanent enrollment halt and decision to no longer pursue the planned study objectives for Parts 1, 2, and 3:

- The investigators were instructed prior to the implementation of the amended protocol version 08 to not collect pharmacokinetic, immunogenicity and pharmacodynamic samples from subjects in core Part 1 in all treatment arms to reduce subject burden. The assessments not performed in the Part 1 core study treatment phase because of the enrollment halt prior to the amended protocol version 08 will be reported in the clinical study report. No pharmacokinetic sample collection will be scheduled in the Part 1 extension treatment phase, including those subjects who complete Safety Follow-up visits following the extension treatment phase EOT.
- There is no change in collection of samples in Part 2 as the only randomized patient in Part 2 has discontinued prior to this amendment.

- Part 3 description in Table 8-16 to Table 8-24 is not applicable as Part 3 will not be initiated.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, changes in PK assessments can be listed as one of the risk mitigation procedures.

Note for subjects that will be randomized to the expansion monotherapy Arm 2 (ruxolitinib cessation) in Part 3, the PK, PD and IG sampling (if applicable) will follow the sampling scheme for the respective investigational drug of the chosen study treatment that enters Part 3. In Part 3 of the study, PK/IG collection (and where applicable, PD samples for sabatolimab) is limited to the first 10 subjects in Arm 1, PK samples will be collected for all 10 subjects in Arm 2 (ruxolitinib cessation), however PK samples will not be collected from subjects randomized to the ruxolitinib control Arm 3.

PK parameters will be estimated from individual plasma concentration-time profiles using appropriate methods and software. A detailed description of the planned PK analyses is given in Section 12.5.3.

Table 8-16 PK blood collection log for siremadlin and ruxolitinib combination arm (Part 1, 2 and 3*)

Cycle	Day	Scheduled Time Point (sampling window)	Dose Reference ID		PK Sample No.		Analytes	Part
			siremadlin	ruxolitinib	siremadlin	ruxolitinib		
1	1	Pre-dose/0 h [a]	11	101	101	201	siremadlin, ruxolitinib	1, 2, 3
1	1	0.5 h (± 10 min)	11	101	102	202	siremadlin, ruxolitinib	1, 2, 3
1	1	1 h (± 10 min)	11	101	103	203	siremadlin, ruxolitinib	1, 2, 3
1	1	2 h (± 10 min)	11	101	104	204	siremadlin, ruxolitinib	1, 2, 3
1	1	3 h (± 15 min)	11	101	105	205	siremadlin, ruxolitinib	1, 2, 3
1	1	4 h (± 15 min)	11	101	106	206	siremadlin, ruxolitinib	1, 2, 3
1	1	8 h (± 1h)	11	101	107	207	siremadlin, ruxolitinib	1
1	2	24 h (± 2h) post siremadlin/ pre-AM C1D2 ruxolitinib dose [a]	11	102	108	208	siremadlin, ruxolitinib	1, 2, 3
1	5	Pre-AM dose/0 h [a]	12	103	109	209	siremadlin, ruxolitinib	1, 2, 3
1	5	1 h (± 10 min)	12	103	110	210	siremadlin, ruxolitinib	1, 2, 3
1	5	2 h (± 10 min)	12	103	111	211	siremadlin, ruxolitinib	1, 2, 3

Cycle	Day	Scheduled Time Point (sampling window)	Dose Reference ID		PK Sample No.		Analytes	Part
			siremadlin	ruxolitinib	siremadlin	ruxolitinib		
1	5	3 h (± 15 min)	12	103	112	212	siremadlin, ruxolitinib	1, 2, 3
1	5	4 h (± 15 min)	12	103	113	213	siremadlin, ruxolitinib	1, 2, 3
1	5	8 h (± 1h)	12	103	114	214	siremadlin, ruxolitinib	1
1	6	24 h (± 2h) post siremadlin/ pre-AM C1D6 ruxolitinib dose [a]	12	104	115	215	siremadlin, ruxolitinib	1, 2, 3
1	15	Pre-AM dose/0 h [a]		105		216	ruxolitinib	1
2	1	Pre-AM dose/0 h [a,]	13	106	116	217	siremadlin, ruxolitinib	1
2	1	1 h (± 10 min)	13	106	117	218	siremadlin, ruxolitinib	1
2	1	2 h (± 10 min)	13	106	118	219	siremadlin, ruxolitinib	1
2	1	3 h (± 15 min)	13	106	119	220	siremadlin, ruxolitinib	1
2	1	4 h (± 15 min	13	106	120	221	siremadlin, ruxolitinib	1
2	1	8 h (± 1h)	13	106	121	222	siremadlin, ruxolitinib	1
2	2	24 h (± 2h) post siremadlin/ pre-AM C2D2 ruxolitinib dose [a]	13	107	122	223	siremadlin, ruxolitinib	1
2	5	Pre-AM dose/0 h [a]	14	108	123	224	siremadlin, ruxolitinib	1, 2
2	5	3 h (± 15 min)	14		124		siremadlin	1, 2
2	6	24 h (± 2h) post siremadlin/ pre-AM C1D6 ruxolitinib dose[a]	14	109	125	225	siremadlin, ruxolitinib	1, 2
2	15	Pre-AM dose/0 h [a,]		110		226	ruxolitinib	1
3	1	Pre-AM dose/0 h [a]		111		227	ruxolitinib	1, 2, 3
3	2	Pre-AM dose/0 h [a]	15		126		siremadlin	1, 2, 3
3	5	Pre-AM dose/0 h [a]	16	112	127	228	siremadlin, ruxolitinib	1, 2, 3

Cycle	Day	Scheduled Time Point (sampling window)	Dose Reference ID		PK Sample No.		Analytes	Part
			siremadlin	ruxolitinib	siremadlin	ruxolitinib		
3	15	Pre-AM dose/0 h [a,]		113		229	ruxolitinib	1
4	1	Pre-AM dose/0 h [a]		114		230	ruxolitinib	1, 2, 3
4	2	Pre-AM dose/0 h [a]	17		128		siremadlin	1, 2, 3
4	5	Pre-AM dose/0 h [a]	18	115	129	231	siremadlin, ruxolitinib	1, 2, 3
5	1	Pre-AM dose/0 h [a]		116		232	ruxolitinib	1, 2, 3
5	2	Pre-AM dose/0 h [a]	19		130		siremadlin	1, 2, 3
5	5	Pre-AM dose/0 h [a]	20	117	131	234	siremadlin, ruxolitinib	1, 2, 3
6	1	Pre-AM dose/0 h [a]		118		235	ruxolitinib	1, 2, 3
6	2	Pre-AM dose/0 h [a]	21		132		siremadlin	1, 2, 3
6	5	Pre-AM dose/0 h [a]	22	119	133	236	siremadlin, ruxolitinib	1, 2, 3
NA	NA	Unscheduled Anytime [b]	NA	NA	1001+	2001+	siremadlin, ruxolitinib	1, 2, 3

[a] Collect PK sample immediately prior to administration

[b] Unscheduled PK blood samples may be collected at any time for measurement of plasma drug concentrations if clinically indicated or at the Investigator's discretion and will be uniquely identified

[*] For Part 3, PK collection limited to first 10 enrolled subjects

Table 8-17 PK blood collection log for crizanlizumab and IG in combination arm with ruxolitinib (Part 1, 2 and 3*)

Cycle	Day	Scheduled Time Point (sampling window)	Dose Reference ID	PK Sample No. (crizanlizumab)	IG Sample No. (IG)	Analytes
1	1	0 h / Pre-infusion [a]	301	601	701	crizanlizumab, IG [d]
1	1	1h post EOI (± 15min) [b]	301	602		crizanlizumab,
1	2	24h post start of infusion (± 2h) [c]	301	603		crizanlizumab,
1	8	168h post start of infusion (± 8h) [c]	301	604		crizanlizumab,
1	15	Pre-infusion of next dose [a] /336h (day 15) post start of infusion (± 24h)	322/301**	605		crizanlizumab,
1	15	1h post EOI (± 15min) [b]	322	606		crizanlizumab,

Cycle	Day	Scheduled Time Point (sampling window)	Dose Reference ID	PK Sample No. (crizanlizumab)	IG Sample No. (IG)	Analytes
2	1	0 h / Pre-infusion [a]	302/322**	607	702	crizanlizumab, IG [d]
2	1	1h post EOI (± 15min) [b]	302	608		crizanlizumab
3	1	0 h / Pre-infusion [a]	303/302**	609	703	crizanlizumab, IG [d]
3	1	1h post EOI (± 5min) [b]	303	610		crizanlizumab,
3	2	24h post start of infusion (± 2h) [c]	303	611		crizanlizumab,
3	8	168h post start of infusion (± 8h) [c]	303	612		crizanlizumab,
3	15	336h post start of infusion (±24h) [c]	303	613		crizanlizumab,
4	1	0 h / Pre-infusion [a]	304/303**	614	704	crizanlizumab, IG [d]
4	1	1h post EOI (± 15min) [b]	304	615		crizanlizumab
5	1	0 h / Pre-infusion [a]	305/304**	616	705	crizanlizumab, IG [d]
5	1	1h post EOI (± 15min) [b]	305	617		crizanlizumab
6	1	0 h / Pre-infusion [a]	306/305**	618	706	crizanlizumab, IG [d]
6	1	1h post EOI (± 15min) [b]	306	619		crizanlizumab
Every 3 Cycles after C6D1 until discontinuation of study treatment	1	0 h / Pre-infusion [a]	307[e]	620[f]	707[g]	crizanlizumab, IG [d]
EOT Core treatment phase		Anytime	NA	6000	7000	crizanlizumab, IG [d]
105-day safety follow-up period		Anytime	NA	6001	7001	crizanlizumab, IG [d]
Unscheduled [h]		Anytime	NA	6002+	7002+	crizanlizumab, IG d

EOI = end of infusion

.** The first Dose Reference ID (for e.g. 302) is for the current dose, while the second Dose Reference ID (for e.g. 301) is for the last (previous) dose received prior to the collection of the PK sample

a Pre-dose: blood samples should be collected prior to the start of the infusion

b Post-dose: sampling time is relative to the end of the infusion; and blood samples should be taken after completion of the infusion

c Post-dose: sampling time is relative to the start of the infusion

d IG samples are to be collected together with PK samples at the same time

e Dose reference ID will be labeled sequentially from 307, 308, 309.....before EOT

Cycle	Day	Scheduled Time Point (sampling window)	Dose Reference ID	PK Sample No. (crizanlizumab)	IG Sample No. (IG)	Analytes
f PK sample will be labeled sequentially from 620, 621, 622.....before EOT g IG sample will be labeled sequentially from 707, 708, 709.....before EOT h Unscheduled PK blood samples may be collected at any time for measurement of plasma drug concentrations if clinically indicated or at the Investigator's discretion and will be uniquely identified * For Part 3, PK/IG collection limited to first 10 enrolled subjects Note: PK and IG blood samples are collected from the opposite arm of infusion site. Alternatively, infusion site will need to be flushed with 10 mL of saline.						

Table 8-18 PK blood collection log for sabatolimab, soluble TIM-3 and IG in combination arm with ruxolitinib (Part 1, 2 and 3*)

Cycle	Day	Scheduled Time Point (sampling window)	Dose Reference ID	PK Sample No. (sabatolimab)	PD Sample No. (TIM-3)	IG Sample No. (IG)	Analyte
1	1	0 h / Pre-infusion [a]	201	301	401	501	sabatolimab, TIM-3, IG [d]
1	1	1h post EOI (± 15min) [b]	201	302	402		sabatolimab, TIM-3 [d]
1	2	24h post start of infusion (± 2h) [c]	201	303	403		sabatolimab, TIM-3 [d]
1	8	168h post start of infusion (± 8h) [c]	201	304	404		sabatolimab, TIM-3 [d]
1	15	336h post start of infusion (± 24h) [c]	201	305	405		sabatolimab, TIM-3 [d]
2	1	0 h / Pre-infusion [a]	202/201**	306	406	502	sabatolimab, TIM-3, IG [d]
2	1	1h post EO (± 15min) [b]	202	307			sabatolimab
3	1	0 h / Pre-infusion [a]	203/202**	308	407	503	sabatolimab, TIM-3, IG [d]
3	1	1h post EOI (± 15min) [b]	203	309	408		sabatolimab, TIM-3 [d]
3	2	24h post start of infusion (± 2h) [c]	203	310	409		sabatolimab, TIM-3 [d]
3	8	168h post start of infusion (± 8h) [c]	203	311	410		sabatolimab, TIM-3 [d]
3	15	336h post start of infusion (± 24h) [c]	203	312	411		sabatolimab, TIM-3 [d]
4	1	0 h / Pre-infusion [a]	204/203**	313	412	504	sabatolimab, TIM-3, IG [d]
4	1	1h post EOI (± 15min) [b]	204	314			sabatolimab
5	1	0 h / Pre-infusion [a]	205/204**	315	413	505	sabatolimab, TIM-3, IG [d]

Cycle	Day	Scheduled Time Point (sampling window)	Dose Reference ID	PK Sample No. (sabatolimab)	PD Sample No. (TIM-3)	IG Sample No. (IG)	Analyte
5	1	1h post EOI (± 15min) [b]	205	316			sabatolimab
6	1	0 h / Pre-infusion [a]	206/205**	317	414	506	sabatolimab, TIM-3, IG [d]
6	1	1h post EOI (± 15min) [b]	206	318			sabatolimab
Every 3 Cycles after C6D1 until discontinuation of study treatment	1	0 h / Pre-infusion [a]	207[e]	319[f]	415[g]	507[h]	sabatolimab, TIM-3, IG [d]
EOT Core treatment phase		Anytime	NA	3000	4000	5000	sabatolimab, TIM-3, IG [d]
90-day safety follow-up period		Anytime	NA	3001		5001	sabatolimab, IG [d]
Unscheduled [i]		Anytime	NA	3002+	4001+	5002+	sabatolimab, TIM-3, IG [d]

EOI = end of infusion

** The first Dose Reference ID (for e.g. 202) is for the current dose, while the second Dose Reference ID (for e.g. 201) is for the last (previous) dose received prior to the collection of the PK sample.

[a] Pre-dose: blood samples should be collected prior to the start of the infusion

[b] Post-dose: sampling time is relative to the end of the infusion; and blood samples should be taken after completion of the infusion

[c] Post-dose: sampling time is relative to the start of the infusion

[d] IG and/or TIM-3 samples are to be collected together with PK samples at the same time

[e] Dose reference ID will be labeled sequentially from 207, 208, 209.....before EOT

[f] PK sample will be labeled sequentially from 319, 320, 221.....before EOT

[g] PD sample will be labeled sequentially from 415, 416, 417.....before EOT

[h] IG sample will be labeled sequentially from 507, 508, 509.....before EOT

[i] Unscheduled PK blood samples may be collected at any time for measurement of plasma drug concentrations if clinically indicated or at the Investigator's discretion and will be uniquely identified

[*] For Part 3, PK, PD and IG collection limited to first 10 enrolled subjects

Note: PK/IG/TIM-3 blood samples are collected from the opposite arm of infusion site. Alternatively, infusion site will need to be flushed with 10 mL of saline.

Table 8-19 PK blood collection log for ruxolitinib in combination arm with crizanlizumab (Part 1, 2 and 3*)

Cycle	Day	Scheduled Time Point (sampling window)	Dose Reference ID	PK Sample No.	Analytes	Part
1	1	Pre-dose/0 h [a]	501	1501	ruxolitinib	1, 2, 3
1	1	0.5 h (± 10 min)	501	1502	ruxolitinib	1, 2, 3
1	1	1 h (± 10 min)	501	1503	ruxolitinib	1, 2, 3
1	1	2 h (± 10 min)	501	1504	ruxolitinib	1, 2, 3
1	1	3 h (± 15 min)	501	1505	ruxolitinib	1, 2, 3
1	1	4 h (± 15 min)	501	1506	ruxolitinib	1, 2, 3

Cycle	Day	Scheduled Time Point (sampling window)	Dose Reference ID	PK Sample No.	Analytes	Part
1	1	8 h (± 1h)	501	1507	ruxolitinib	1, 2, 3
1	2	Pre-AM dose/0 h [a]	502	1508	ruxolitinib	1, 2, 3
1	15	Pre-AM dose/0 h [a]	503	1509	ruxolitinib	1
2	1	Pre-AM dose/0 h [a]	504	1510	ruxolitinib	1, 2, 3
2	15	Pre-AM dose/0 h [a]	505	1511	ruxolitinib	1
3	1	Pre-AM dose/0 h [a]	506	1512	ruxolitinib	1, 2, 3
3	15	Pre-AM dose/0 h [a]	507	1513	ruxolitinib	1
4	1	Pre-AM dose/0 h [a]	508	1514	ruxolitinib	1, 2, 3
5	1	Pre-AM dose/0 h [a]	509	1515	ruxolitinib	1, 2, 3
6	1	Pre-AM dose/0 h [a]	510	1516	ruxolitinib	1, 2, 3
NA	NA	Unscheduled Anytime [b]	NA	1601+	ruxolitinib	1, 2, 3

[a] Collect PK sample immediately prior to administration

[b] Unscheduled PK blood samples may be collected at any time for measurement of plasma drug concentrations if clinically indicated or at the Investigator's discretion and will be uniquely identified

[*] For part 3, PK collection limited to first 10 enrolled subjects

Table 8-20 PK blood collection log for ruxolitinib in combination arm with sabatolimab (Part 1, 2 and 3*)

Cycle	Day	Scheduled Time Point (sampling window)	Dose Reference ID	PK Sample No.	Analytes	Part
1	1	Pre-dose/0 h [a]	401	801	ruxolitinib	1, 2, 3
1	1	0.5 h (± 10 min)	401	802	ruxolitinib	1, 2, 3
1	1	1 h (± 10 min)	401	803	ruxolitinib	1, 2, 3
1	1	2 h (± 10 min)	401	804	ruxolitinib	1, 2, 3
1	1	3 h (± 15 min)	401	805	ruxolitinib	1, 2, 3
1	1	4 h (± 15 min)	401	806	ruxolitinib	1, 2, 3
1	1	8 h (± 1h)	401	807	ruxolitinib	1, 2, 3
1	2	Pre-AM dose/0 h [a]	402	808	ruxolitinib	1, 2, 3
1	15	Pre-AM dose/0 h [a]	403	809	ruxolitinib	1
2	1	Pre-AM dose/0 h [a]	404	810	ruxolitinib	1, 2, 3
2	15	Pre-AM dose/0 h [a]	405	811	ruxolitinib	1
3	1	Pre-AM dose/0 h [a]	406	812	ruxolitinib	1, 2, 3
3	15	Pre-AM dose/0 h [a]	407	813	ruxolitinib	1
4	1	Pre-AM dose/0 h [a]	408	814	ruxolitinib	1, 2, 3
5	1	Pre-AM dose/0 h [a]	409	815	ruxolitinib	1, 2, 3
6	1	Pre-AM dose/0 h [a]	410	816	ruxolitinib	1, 2, 3
NA	NA	Unscheduled Anytime [b]	NA	8001+	ruxolitinib	1, 2, 3

[a] Collect PK sample immediately prior to administration

[b] Unscheduled PK blood samples may be collected at any time for measurement of plasma drug concentrations if clinically indicated or at the Investigator's discretion and will be uniquely identified

[*] For part 3, PK collection limited to first 10 enrolled subjects

Table 8-21 PK blood collection log for ruxolitinib (single agent control arm) in Part 2 ONLY

Cycle	Day	Scheduled Time Point (sampling window)	Dose Reference ID	PK Sample No.	Analytes
1	1	Pre-dose/0 h [a]	601	901	ruxolitinib
1	1	0.5 h (± 10 min)	601	902	ruxolitinib
1	1	1 h (± 10 min)	601	903	ruxolitinib
1	1	2 h (± 10 min)	601	904	ruxolitinib
1	1	3 h (± 15 min)	601	905	ruxolitinib
1	1	4 h (± 15 min)	601	906	ruxolitinib
1	1	8 h (± 1h)	601	907	ruxolitinib
2	1	Pre-AM dose/0 h [a]	604	910	ruxolitinib
3	1	Pre-AM dose/0 h [a]	606	912	ruxolitinib
4	1	Pre-AM dose/0 h [a]	608	914	ruxolitinib
5	1	Pre-AM dose/0 h [a]	609	915	ruxolitinib
6	1	Pre-AM dose/0 h [a]	610	916	ruxolitinib
NA	NA	Unscheduled Anytime [b]	NA	9001+	ruxolitinib

[a] Collect PK sample immediately prior to administration

[b] Unscheduled PK blood samples may be collected at any time for measurement of plasma drug concentrations if clinically indicated or at the Investigator's discretion and will be uniquely identified

Table 8-22 PK blood collection log for rineterkib and ruxolitinib combination arm (Part 1, 2 and 3*)

Cycle	Day	Scheduled Time Point (sampling window)	Dose Reference ID		PK Sample No.		Analytes	Part
			rineterkib	ruxolitinib	rineterkib	ruxolitinib		
1	1	Pre-dose/0 h [a]	701	801	2501	3501	rineterkib, ruxolitinib	1, 2, 3
1	1	0.5 h (± 10 min)	701	801	2502	3502	rineterkib, ruxolitinib	1, 2, 3
1	1	1 h (± 10 min)	701	801	2503	3503	rineterkib, ruxolitinib	1, 2, 3
1	1	2 h (± 10 min)	701	801	2504	3504	rineterkib, ruxolitinib	1, 2, 3
1	1	3 h (± 15 min)	701	801	2505	3505	rineterkib, ruxolitinib	1, 2, 3
1	1	4 h (± 15 min)	701	801	2506	3506	rineterkib, ruxolitinib	1, 2, 3
1	1	8 h (± 1h) [c]	701	801	2507	3507	rineterkib, ruxolitinib	1
1	2	24 h (± 2h) post LTT462 / pre-AM C1D2 [a]	701/702	802	2508	3508	rineterkib, ruxolitinib	1
1	15	Pre-AM dose/0 h [a]	703	803	2509	3509	rineterkib, ruxolitinib	1, 2, 3
1	15	0.5 h (± 10 min)	703	803	2510	3510	rineterkib, ruxolitinib	1, 2, 3
1	15	1 h (± 10 min)	703	803	2511	3511	rineterkib, ruxolitinib	1, 2, 3

Cycle	Day	Scheduled Time Point (sampling window)	Dose Reference ID		PK Sample No.		Analytes	Part
			rineterkib	ruxolitinib	rineterkib	ruxolitinib		
1	15	2 h (± 10 min)	703	803	2512	3512	rineterkib, ruxolitinib	1, 2, 3
1	15	3 h (± 15 min)	703	803	2513	3513	rineterkib, ruxolitinib	1, 2, 3
1	15	4 h (± 15 min)	703	803	2514	3514	rineterkib, ruxolitinib	1, 2, 3
1	15	8 h (± 1h) [c]	703	803	2515	3515	rineterkib, ruxolitinib	1
1	16	24 h (± 2h) post LTT462 / pre-AM C1D16 [a,c]	703/704	804	2516	3516	rineterkib, ruxolitinib	1
2	1	Pre-AM dose/0 h [a]	705	805	2517	3517	rineterkib, ruxolitinib	1, 2, 3
3	1	Pre-AM dose/0 h [a]	706	806	2518	3518	rineterkib, ruxolitinib	1, 2, 3
4	1	Pre-AM dose/0 h [a]	707	807	2519	3519	rineterkib, ruxolitinib	1, 2, 3
5	1	Pre-AM dose/0 h [a]	708	808	2520	3520	rineterkib, ruxolitinib	1, 2, 3
6	1	Pre-AM dose/0 h [a]	709	809	2521	3521	rineterkib, ruxolitinib	1, 2, 3
NA	NA	Unscheduled Anytime [b]	NA	NA	2601+	3601+	rineterkib, ruxolitinib	1, 2, 3

[a] Collect PK sample immediately prior to administration

[b] Unscheduled PK blood samples may be collected at any time for measurement of plasma drug concentrations if clinically indicated or at the Investigator's discretion and will be uniquely identified

[c] PK sampling time point not collected for Part 2 and 3

[*] For Part 3, PK collection limited to first 10 enrolled subjects

Table 8-23 PK blood collection log for NIS793 and IG in combination arm with ruxolitinib (Part 1, 2 and 3*)

Cycle	Day	Scheduled Time Point (h)**	Dose Reference ID	PK Sample No.	IG Sample No.*	Analyte	Part
1	1	0 h / Pre-infusion [a]	901	4501	5501	NIS793, IG [d]	1, 2, 3
1	1	1h post EOI (± 15min) [b]	901	4502		NIS793	1, 2, 3
1	2	24 h post start of infusion (+ 2h) [c]	901	4503		NIS793	1, 2, 3
1	4	72h post start of infusion (± 8h) [c]	901	4504		NIS793	1
1	8	168h post start of infusion (± 8h) [c]	901	4505		NIS793	1, 2, 3
1	11	240h post start of infusion (± 24h) [c]	901	4506		NIS793	1

Cycle	Day	Scheduled Time Point (h)**	Dose Reference ID	PK Sample No.	IG Sample No.*	Analyte	Part
1	15	336h post start of infusion (± 24h) [c]	901	4507		NIS793	1, 2, 3
2	1	504h post start of infusion (± 48h) (Pre-infusion of cycle 2)	901/902	4508	5502	NIS793, IG [d]	1, 2, 3
3	1	0 h / Pre-infusion [a]	903	4509	5503	NIS793, IG [d]	1, 2, 3
3	1	1h post EOI (± 15 min) [b]	903	4510		NIS793	1, 2, 3
3	2	24 h post start of infusion (+ 2h) [c]	903	4511		NIS793	1, 2, 3
3	4	72h post start of infusion (± 8h) [c]	903	4512		NIS793	1
3	8	168h post start of infusion (± 8h) [c]	903	4513		NIS793	1, 2, 3
3	11	240h post start of infusion (± 24h) [c]	903	4514		NIS793	1
3	15	336h post start of infusion (± 24h) [c]	903	4515		NIS793	1, 2, 3
4	1	504h post start of infusion (± 48h) (Pre-infusion of cycle 4)	903/904	4516	5504	NIS793, IG [d]	1, 2, 3
5	1	0 h / Pre-infusion [a]	905	4517	5505	NIS793, IG [d]	1, 2, 3
6	1	0 h / Pre-infusion [a]	906	4518	5506	NIS793, IG [d]	1, 2, 3
6	1	1h post EOI (± 15 min) [b]	906	4519	-	NIS793	1, 2, 3
7	1	0 h / Pre-infusion [a]	907	4520	5507	NIS793, IG [d]	1, 2, 3
8	1	0 h / Pre-infusion [a]	908	4521	5508	NIS793, IG [d]	1, 2, 3
Every 4 Cycles after C8D1 until discontinuation of study treatment	1	0 h / Pre-infusion [a]	909 [e]	4522 [f]	5509 [g]	NIS793, IG [d]	1, 2, 3
EOT Core treatment phase		Anytime	NA	10000	20000	NIS793, IG [d]	1, 2, 3
Safety follow-up Day 30		Anytime	NA	10001	20001	NIS793, IG [d]	1, 2, 3
Safety follow-up Day 90		Anytime	NA	10002	20002	NIS793, IG [d]	1, 2, 3
Unscheduled [h]		Anytime	NA	10003+	20003+	NIS793, IG [d]	1, 2, 3
EOI = end of infusion							

Cycle	Day	Scheduled Time Point (h)**	Dose Reference ID	PK Sample No.	IG Sample No.*	Analyte	Part

** The first Dose Reference ID (for e.g. 902) is for the current dose, while the second Dose Reference ID (for e.g. 901) is for the last (previous) dose received prior to the collection of the PK sample

[a] Pre-dose: blood samples should be collected prior to the start of the infusion

[b] Post-dose: sampling time is relative to the end of the infusion; and blood samples should be taken after completion of the infusion

[c] Post-dose: sampling time is relative to the start of the infusion

[d] IG samples are to be collected together with PK samples at the same time

[e] Dose reference ID will be labeled sequentially from 910, 911, 912.....before EOT

[f] PK sample will be labeled sequentially from 4523, 4524, 4525.....before EOT

[g] IG sample will be labeled sequentially from 5510, 5511, 5512.....before EOT

[h] Unscheduled PK blood samples may be collected at any time for measurement of plasma drug concentrations if clinically indicated or at the Investigator's discretion and will be uniquely identified

* For Part 3, IG/PK collection limited to first 10 enrolled subjects

Note: PK and IG blood samples are collected from the opposite arm of infusion site. Alternatively, infusion site will need to be flushed with 10 mL of saline.

Table 8-24 PK blood collection log for ruxolitinib in combination arm with NIS793 (Part 1, 2 and 3*)

Cycle	Day	Scheduled Time Point (sampling window)	Dose Reference ID	PK Sample No.	Analyte
1	1	Pre-dose/0 h [a]	1001	6501	ruxolitinib
1	1	0.5 h (± 10 min)	1001	6502	ruxolitinib
1	1	1 h (± 10 min)	1001	6503	ruxolitinib
1	1	2 h (± 10 min)	1001	6504	ruxolitinib
1	1	3 h (± 15 min)	1001	6505	ruxolitinib
1	1	4 h (± 15 min)	1001	6506	ruxolitinib
1	1	8 h (± 1h)	1001	6507	ruxolitinib
2	1	Pre-AM dose/0 h a	1002	6508	ruxolitinib
3	1	Pre-AM dose/0 h a	1003	6509	ruxolitinib
4	1	Pre-AM dose/0 h a	1004	6510	ruxolitinib
5	1	Pre-AM dose/0 h a	1005	6511	ruxolitinib
6	1	Pre-AM dose/0 h [a]	1006	6512	ruxolitinib
7	1	Pre-AM dose/0 h [a]	1007	6513	ruxolitinib
8	1	Pre-AM dose/0 h [a]	1008	6514	ruxolitinib
NA	NA	Unscheduled Anytime [b]	NA	30001+	ruxolitinib

[a] Collect PK sample immediately prior to administration

[b] Unscheduled PK blood samples may be collected at any time for measurement of plasma drug concentrations if clinically indicated or at the Investigator's discretion and will be uniquely identified

[*] For part 3, PK collection limited to first 10 enrolled subjects

8.5.2.1 Pharmacokinetic, [redacted] immunogenicity blood collection and handling

Blood samples for ruxolitinib PK evaluation will be collected from all subjects who receive at least one dose of ruxolitinib, except as follows: PK samples will only be collected from the first 10 subjects of the 20 subjects randomized into the combination treatment arm (Arm 1) of

Part 3 (d), and no PK samples will be collected from the ruxolitinib control arm (Arm 3) of Part 3 of the study. The time points of blood collection for ruxolitinib PK are outlined in Table 8-16, Table 8-19, Table 8-20, Table 8-21, Table 8-22 and Table 8-24 .

Blood samples for siremadlin PK evaluation will be collected from all subjects who receive at least one dose of siremadlin. Time points of blood collection for siremadlin PK are outlined in Table 8-16, along with the time points of blood collection for ruxolitinib PK in combination with siremadlin.

Blood samples for crizanlizumab PK and IG will be collected from all subjects who receive at least one dose of crizanlizumab. Time points of blood collection for crizanlizumab PK and IG are outlined in Table 8-17. The time points of blood collection for ruxolitinib PK in combination with crizanlizumab are outlined in Table 8-19.

Blood samples for sabatolimab PK, IG and PD (TIM-3) will be collected from all subjects who receive at least one dose of sabatolimab. Time points of blood collection for sabatolimab PK, IG and TIM-3 are outlined in Table 8-18. The time points of blood collection for ruxolitinib PK in combination with sabatolimab are outlined in Table 8-20.

Blood samples for rineterkib PK evaluation will be collected from all subjects who receive at least one dose of rineterkib. Time points of blood collection for rineterkib PK are outlined in Table 8-22 , along with the the time points of blood collection for ruxolitinib PK in combination with rineterkib.

Blood samples for NIS793 PK and IG will be collected from all subjects who receive at least one dose of NIS793. Time points of blood collection for NIS793 PK and IG are outlined in Table 8-23 . The time points of blood collection for ruxolitinib PK in combination with NIS793 are outlined in Table 8-24 .

On days of sample blood collection, subjects should take their medication at the clinic immediately after the first blood sample (e.g., pre-dose/0 hr sample). The exact dates and clock times of study drug administration and sample blood collection will be recorded on the appropriate CRF. Any sampling issues should be noted on the CRF and on appropriate source documentation.

Blood samples will be collected by either direct venipuncture or an indwelling cannula inserted in a forearm vein opposite to the arm used for study drug infusion (in the case of sabatolimab crizanlizumab or NIS793). For ruxolitinib, a total of 2.5 mL of blood will be collected for PK analysis in plasma. For siremadlin and rineterkib, a total of 2 mL of blood will be collected for PK analysis in plasma. For crizanlizumab, a total of 2.5 and 3.5 mL of blood will be collected for PK and IG analysis in serum, respectively. For sabatolimab, a total of 1 mL of blood will each be collected for PK and TIM-3 analysis in serum, while a total of 2 mL of blood will be collected for IG analysis in serum. For NIS793, a total of 6 mL of blood will each be collected for PK and IG analysis in serum. For time points when sampling of mAb (sabatolimab, crizanlizumab or NIS793) PD or IG coincide with PK, a single blood sample of the appropriate volume will be collected for PD or IG and PK.

Additional PK, PD and IG samples will be collected at EOT from subjects treated with crizanlizumab, sabatolimab, and NIS793. Additional PK and IG samples will be collected at the 90-day safety follow up visit from subjects treated with sabatolimab, or at the 105-day safety

follow up visit from subjects treated with crizanlizumab. Additional PK, PD and IG samples will be collected at the 30-day and 90-day safety follow up visits for subjects treated with NIS793. Not applicable from amended protocol version 08. The assessments not performed in the study treatment phase because of the enrollment halt prior to the implementation of amended protocol version 08 will be documented for transparency in the clinical study report.

If subjects experience a DLT, SAE or an AE leading to the discontinuation of the study treatment, an unscheduled PK blood sample should be obtained as close as possible to the event occurrence. If patients experience a suspected immune-related AE such as infusion-related reaction, hypersensitivity, cytokine release syndrome and anaphylaxis, an unscheduled IG blood sample should be obtained as close as possible to the event occurrence. The date and time of the last dose and the time of PK blood draw should be recorded.

[redacted]

Refer to the study [Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK, IG and PD samples.

8.5.2.2 Analytical method

Bioanalysis for PK, IG or PD samples will employ the following validated assays:

1. Plasma concentrations of rineterkib, siremadlin and ruxolitinib will be determined using a validated LC-MS/MS assay, with a current LLOQ of 1 ng/mL, 1 ng/mL and 0.5 ng/mL, respectively.
2. Serum concentrations of crizanlizumab will be determined using a validated target capture enzyme-linked immunosorbent assay (ELISA).
3. Serum concentrations of sabatolimab will be determined using a validated LC-MS assay, with a current LLOQ of 5.0 µg/mL.
4. Anti-crizanlizumab antibodies will be evaluated in serum using a validated Meso Scale Discovery (MSD) electrochemiluminescence assay and anti-sabatolimab antibodies will evaluated in serum using a validated ELISA.
5. Serum concentrations of total TIM-3 will be determined using a validated ELISA.
6. The assay to quantify NIS793 will be a validated sandwich ELISA.
7. The assay to quantify and assess the IG against NIS793 will be a validated Meso Scale Discovery (MSD) electrochemiluminescence assay.

Details of each analytical method will be documented in the bioanalytical data reports.

[redacted]

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the subject or the investigator.

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

Study treatment must be discontinued under the following circumstances:

- Subject/guardian decision
- Pregnancy
- Investigator decision, including lack of clinical benefit
- Disease progression (refer to definition in Section 8.3.2.5)
- Adverse events leading to study treatment discontinuation
- Protocol deviations that result in a significant risk to the subject's safety including the use of prohibited treatment and any dose holds greater than 21 days for arms containing NIS793 or 28 days for all other arms
- New anti-neoplastic therapy for study indication
- Subjects who are scheduled for ASCT at any time during the course of the study

In addition to the above, study treatment should be discontinued under the following circumstances during the extension treatment phase:

- Subject is no longer deriving clinical benefit from study treatment in the opinion of the investigator.
- Subject has local access to alternative treatment for study indication including those currently under investigation in clinical trials as assessed suitable in the opinion of the investigator.
- Subject withdraws consent.

Subject enrolls in another interventional study.If discontinuation of study treatment occurs, the Investigator should make a reasonable effort to understand the primary reason for the subject's premature discontinuation of study treatment and record this information.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see 'Withdrawal of Informed Consent' section). Where possible, all subjects should return for and End of Treatment (EOT) visit within 7 days after discontinuation of permanent study treatment (all investigational drugs), at which time all of the assessments for EOT indicated in Table 8-2, Table 8-3, Table 8-4, or Table 8-5 should be performed, including a physical examination, vital signs, height, weight, ECOG performance status, ECG, concomitant medications, non-drug therapy and procedures, collection of AEs and any transfusions, laboratory assessments, spleen palpation (CT or MRI imaging, blood sampling for PK/PD [redacted], bone marrow biopsy or aspirate, and, if applicable, immunogenicity for crizanlizumab, sabatolimab or NIS793. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up Section 9.1.3. This contact should preferably be done according to the study visit schedule.

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, all subjects must have a Safety Follow-up visit 30 days after permanent study treatment discontinuation as described in Section 9.2.

The investigator must also contact the IRT to register the subject's discontinuation from study treatment.

9.1.1.1 Replacement policy

Part 1 (Dose escalation and safety run-in)

Subjects will not be replaced on study. However, if a subject is considered as non-evaluable for the DDS, enrollment of a new subject to the current cohort will be considered if there is less than the required number of evaluable subjects. Enrollment of new subjects may be considered until at least the minimum number (3) or at most the maximum number (6) of evaluable subjects is achieved within the cohort. Minimum and maximum numbers of evaluable subjects per cohort are defined in the guidelines for dose escalation and determination section (Section 6.5.2).

Part 2 and Part 3 (Selection and expansion)

During the selection and expansion parts of the study no replacements will be needed.

9.1.2 Withdrawal of informed consent/Opposition to use data/biological samples

Withdrawal of consent/opposition to use data/biological samples occurs when a subject:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples)

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be in writing (depending on local regulations) and recorded in the source documentation.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the participant therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

If the subject agrees, a final evaluation at the time of the subject's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table.

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed.

Subjects considered to be lost to follow-up should be recorded as such on the appropriate Disposition eCRF.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate the study, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be contacted and seen as soon as possible to stop study treatment, and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion

All subjects receiving combination treatment must have a Safety Follow-up visit at least 30 days (+7 days) after the last dose of study treatment (all investigational drugs) to have hematology, chemistry, vital signs and serum pregnancy assessments and to collect information on any AEs, concomitant medications, transfusions, non-drug therapies and procedures, and anti-neoplastic therapies. Additional Safety Follow-up visits should also occur, as follows:

- 105 days (+7 days) after the last dose of crizanlizumab for subjects on ruxolitinib + crizanlizumab (or crizanlizumab monotherapy in Part 3)
- 90 days (+7 days), and 150 days (+14 days) after the last dose of sabatolimab for subjects on ruxolitinib + sabatolimab (or sabatolimab monotherapy in Part 3).
- 90 days (+7 days) after the last dose of NIS793 for subjects on ruxolitinib + NIS793 (or NIS793 monotherapy in Part 3).

The timing of the final Safety Follow-up visit is based on a period of at least 5 times the half-life of crizanlizumab, sabatolimab, and NIS792 after the last dose when the serum level of

crizanlizumab, sabatolimab, and NIS793 in all subjects should be negligible or below the LLOQ.

At the 90-, 105-, and 150-day Safety Follow-up visits, the same assessments will be performed as per the 30-day Safety Follow-up visit. The planned PK sample and IG sample will not be collected at the 90-day Safety Follow-up visit for sabatolimab, and at the 105-day Safety Follow-up visit for crizanlizumab, due to enrollment halt. For NIS793, the planned PK, PD and IG samples will not be collected at the 30-day and 90-day Safety Follow-up visits, due to enrollment halt. However, if the subject begins new antineoplastic medication (other than study treatment) before the end of the safety follow-up period, the collection of new SAEs and AEs unrelated to study medication will stop and thereafter only suspected AEs and suspected SAEs will continue to be collected up to the end of the safety follow-up period.

Refer to Table 8-2, Table 8-3, Table 8-4 and Table 8-5 for a complete list of the assessments to be completed at the Safety Follow-up visits. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the subject should be recorded in the source documentation.

Subjects in Part 2 and Part 3 of the study will also be contacted by telephone every 3 months (12 weeks +/- 14 days) after study treatment discontinuation to follow-up on the survival status, any new anti-neoplastic therapies (including transfusions), and leukemic transformation. See Table 8-3 and Table 8-5 for details.

Due to enrollment halt, the primary analysis will be conducted after the last subject performed the eEOT for core treatment phase in Part 1 and after Part 1 and 2 subjects have received at least 8 cycles (for arms with NIS793) or 6 cycles of treatment (for all other arms) or discontinued earlier. The primary analysis data will be summarized in the primary clinical study report (CSR). Following the cut-off date for the analysis reported in the primary CSR, the study will remain open until the end of the study. Ongoing subjects may continue to receive study treatment in the extension treatment phase and be followed as per the schedule of assessments, as long as subjects derive benefit from the study treatment.

The end of study (study completion) will occur after the last subject has completed the extension treatment phase (21 cycles of extension treatment), or earlier if all subjects have died or discontinued from the study (provided that all required safety follow-up visits have occurred). The final analysis will occur at the end of the study. All available extension treatment phase data up to this cut-off date will be analyzed and reported in a final CSR.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the

study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0
2. Its relationship to the study treatments. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment. All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed
   - Dose reduced
   - Drug interrupted/withdrawn
6. Its outcome (i.e. recovery status or whether it was fatal)

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

Conditions that were already present at the time of informed consent should be recorded in medical history of the subject.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least:

- 30 days after the last dose of single-agent ruxolitinib (control/monotherapy)
- 30 days after the last dose of ruxolitinib or siremadlin for subjects on ruxolitinib + siremadlin (or siremadlin monotherapy in Part 3)
- 30 days after the last dose of ruxolitinib or rineterkib for subjects on ruxolitinib + rineterkib (or rineterkib monotherapy in Part 3)
- 90 days after the last dose of NIS793 for subjects on ruxolitinib + NIS793 (or NIS793 monotherapy in Part 3)
- 105 days after the last dose of crizanlizumab for subjects on ruxolitinib + crizanlizumab (or crizanlizumab monotherapy in Part 3)
- 150 days after the last dose of sabatolimab for subjects on ruxolitinib + sabatolimab (or sabatolimab monotherapy in Part 3).

OR

- until the start of a new post treatment anti-neoplastic medication if sooner than the end of the safety follow-up period mentioned above, depending on the study treatment. If a subject starts post treatment antineoplastic medication, then only adverse events suspected to be related to study treatment should be collected, up to the end of the safety follow-up period noted above.

Progression of the underlying disease (myelofibrosis) (including fatal outcomes) based on the criteria described in Section 8.3.2.3 (ie. progressive splenomegaly, increase in peripheral blood blast content of > 10% (accelerated phase), deteriorating cytopenia, leukemic transformation) should not be reported as a serious adverse event. These disease progression events will be reported on specific CRF pages other than the AE CRF.

Adverse events separate from the progression of malignancy (i.e. deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

1. they induce clinical signs or symptoms
2. they are considered clinically significant
3. they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values, which are considered to be non-typical in subjects with the underlying disease.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

1. fatal
2. life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the subject's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are 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 dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred (Section 10.1.5).

Treatment-emergent elevations in AST or ALT (>3x ULN) in combination with total bilirubin >2x ULN or jaundice in the absence of cholestasis (defined as ALP < 2 ULN) or other causes of hyperbilirubinemia can be an indicator of severe drug induced liver injury (Hy's Law).

For this reason, a potential Hy's Law case requires expedited reporting, and will be handled as a serious unexpected adverse event (assessing it as medically significant in the absence of any other seriousness criteria). It must be reported as an SAE to the sponsor promptly (i.e., even before all other possible causes of liver injury have been excluded). Reporting should include all available information, especially that needed for evaluating the diagnosis, severity and likelihood that the study treatment caused the reaction. For patient monitoring and to better understand potential etiologies, the investigator must initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail) until the end of the safety follow-up period, as follows:

- 30 days after the last dose of single-agent ruxolitinib (control/monotherapy)
- 30 days after the last dose of ruxolitinib or siremadlin for subjects on ruxolitinib + siremadlin (or siremadlin monotherapy in Part 3)
- 30 days after the last dose of ruxolitinib or rineterkib for subjects on ruxolitinib + rineterkib (or rineterkib monotherapy in Part 3)
- 90 days after the last dose of NIS793 for subjects on ruxolitinib + NIS793 (or NIS793 monotherapy in Part 3)
- 105 days after the last dose of crizanlizumab for subjects on ruxolitinib + crizanlizumab (or crizanlizumab monotherapy in Part 3),
- 150 days after the last dose of sabatolimab for subjects on ruxolitinib + sabatolimab (or sabatolimab monotherapy in Part 3).

If a subject starts post treatment anti-neoplastic medication then only SAEs suspected to be related to study treatment should be collected, up to the time frame noted above depending on the study treatment (30 days for ruxolitinib, siremadlin or rineterkib, 90 days for NIS793, 105 days for crizanlizumab or 150 days for sabatolimab).

For Screen Failure subjects, SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.

Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Progression of the underlying disease (myelofibrosis) (including fatal outcomes) based on the criteria described in Section 8.3.2.4 (ie. progressive splenomegaly, increase in peripheral blood blast content of > 10% (accelerated phase), deteriorating cytopenia, leukemic transformation) should not be reported as a SAE. As noted in Section 10.1.1, these disease progression events will be reported on specific CRF pages other than the AE CRF.

Any SAEs experienced more than 30 days after the last dose of single-agent ruxolitinib (control/monotherapy), 30 days after the last dose of ruxolitinib + siremadlin, 30 days after the last dose of ruxolitinib + rineterkib, 90 days after the last dose of ruxolitinib + NIS793, 105 days for ruxolitinib + crizanlizumab (or crizanlizumab monotherapy in Part 3), and 150 days after the last dose of ruxolitinib + sabatolimab (or sabatolimab monotherapy in Part 3) should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

If a female subject becomes pregnant, the study treatment should be stopped, and the subject must be asked to read and sign pregnancy consent form to allow the investigator ask about her pregnancy. To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

If the pregnancy results in a live birth, the baby will have regular check-ups and the investigator will need to know the outcomes of these check-ups until one year after the baby was due to be born.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment Error Type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE Form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will be responsible to review safety, PK/PD, DLT and critical efficacy variables data approximately every 6 months (or as needed) during the treatment period (after the first subject has started Part 1 study treatment) and recommend to Novartis whether to continue, modify, or terminate a trial. The DMC will also provide recommendation to the Novartis study team which ruxolitinib treatment combination arm(s) should be further developed in Part 2 and Part 3. As the enrollment was permanently halted, the Part 2 has been prematurely discontinued with one randomized patient, and Part 3 will not be initiated, therefore the descriptions above for Parts 2 and 3 are not applicable.

Specific details regarding composition, responsibilities, data monitoring, and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate DMC Charter that is established between Novartis and the DMC.

10.2.2 Steering Committee

The Steering Committee (SC) will be established comprising investigators participating in the trial, i.e. not being members of the DMC and not Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will provide recommendation to the study team about which ruxolitinib combination treatment arm (s) should be further developed in Part 2 and Part 3. As the enrollment was permanently halted, the Part 2 has been prematurely discontinued with one randomized patient, and Part 3 will not be initiated, therefore the descriptions above for Parts 2 and 3 are not applicable.

The SC will also review protocol amendments as appropriate. Together with the Clinical Trial Team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the steering committee will be defined in the SC Charter.

11 Data Collection and Database management

11.1 Data collection

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

This study will use Electronic Data Capture (EDC). Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data entered into the eCRF is complete, accurate, and that entries and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

Blood samples for some laboratory assessments, [redacted] and PK samples and/or data will be processed centrally and the results will be sent electronically to Novartis as described in the Data Transfer Specifications.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Randomization codes and data about all study treatment(s) dispensed to the subject and all dosage changes will be tracked using an IRT. The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis/delegated CRO representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/delegated CRO/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original ICF signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

All statistical analyses will be performed under the direction of Novartis personnel. Any data analysis carried out independently by the investigator should be submitted to Novartis prior to publication or presentation.

It is planned that the data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for analysis. Data will be summarized with respect to demographic and baseline characteristics, efficacy and safety observations and measurements, and all relevant PK and PD measurements using descriptive statistics (quantitative data) and contingency tables (qualitative data) as appropriate.

Subjects treated at different dose levels of ruxolitinib will be pooled into a single treatment group for each dose level of the combination partners. A treatment group is defined by both combination partner and the dose level of the combination partner (siremadlin arm and rineterkib arm) for Part 1 subjects. A treatment group is defined by the combination partner for Part 2 and Part 3 subjects.

Enrollment was permanently halted and Part 2 was prematurely discontinued with one randomized subject; Part 3 will not be initiated. The primary CSR will include analyses on all subject data at the time when the last subject completed the end of treatment visit for core treatment phase (Part1), and after all subjects have completed at least 8 cycles (arms with NIS793) or 6 cycles (all other arms) of treatment or discontinued earlier (Part 1 and Part 2). All extension treatment phase data will be reported in the final CSR once all subjects are discontinued from the study or completed the extension treatment phase (maximum 21 cycles) whichever comes last. Subjects in Part 1 will be analyzed separately from subjects in Part 2. Data from Part 2 will be listed but not summarized.

Two interim analyses are planned for each combination treatment in Part 2. The first interim analysis is planned when at least 10 subjects have been randomized into each of the treatment and have completed at least 8 cycles (arms with NIS793) or 6 cycles (all other arms) of treatment or discontinued earlier for a seamless transition into Part 3 expansion in the presence of outstanding preliminary efficacy. The second interim analysis is planned when all Part 2 subjects (at least 25 subjects) of each combination treatment arm have completed at least 8 cycles (arms with NIS793) or 6 cycles (all other arms) of treatment or discontinued earlier for advancing the combination treatment in Part 3 that are not futile or stopped for safety. The second interim analysis is not required if a combination treatment is advanced in Part 3 based on the first interim analysis.

Due to the permanent enrollment halt, the description for Parts 2 and 3, including interim analyses are not applicable as outlined in amended protocol version 08.

The primary analysis will be performed on all subjects after the last subject performed the end of treatment visit (EOT) for core treatment phase (Part 1), and after all subjects have completed at least 8 cycles (arms with NIS793) or 6 cycles (all other arms) of treatment or discontinued earlier (Part 1 and Part 2). The final analysis for the extension phase data will be performed at the end of the study.

12.1 Analysis sets

12.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all subjects that received any study drug. Subjects will be analyzed according to the treatment(s) received.

12.1.2 Safety Set

The Safety Set includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment received, where treatment received is defined as the randomized/assigned treatment if the subject took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received.

12.1.3 Dose-Determining Set

The Dose-Determining Set (DDS) includes all subjects from the safety run-in and dose escalation part (Part 1) of the study who met the minimum exposure criterion and had sufficient safety evaluations, or experienced a dose-limiting toxicity (DLT) between C1D1 and C3D1. The minimum exposure required for combination treatments defined as follows:

- For ruxolitinib + rineterkib study treatment arm, a subject has met the minimum exposure criterion if the subject takes at least 75% of the planned daily rineterkib and ruxolitinib combination doses during the first two treatment cycles of dosing, i.e. at least 21 full dosing days out of the planned 28 days for the rineterkib and ruxolitinib combination, and the subject takes at least 80% of the planned daily doses of ruxolitinib i.e. at least 23 full dosing days out of the planned 28 days for ruxolitinib.
- For all other study treatment arms, a subject has met the minimum exposure criterion if the subject takes all planned doses of the combination agent during the first two treatment cycles of dosing, and at least 80% of the planned daily doses of ruxolitinib i.e. at least 23 full dosing days (17 days for NIS793) out of the planned 28 days (21 days for NIS793) for ruxolitinib.

Subjects who do not experience a DLT between C1D1 and C3D1 are considered to have sufficient safety evaluations if they have been observed until C2D28, or C2D21 for the ruxolitinib + NIS793 study treatment arm, and are considered by both the sponsor and investigators to have enough safety data to conclude that a DLT did not occur.

For Japan only: subjects enrolled after the dose determination for a combination treatment will not be included in the DDS.

12.1.4 Pharmacokinetic analysis set

The Pharmacokinetic Analysis Set (PAS) includes all enrolled subjects who have an evaluable PK profile. A profile is considered evaluable if all of the following conditions are satisfied:

- Subject receives the planned treatments
- Subject takes the dose of study treatments as described in Section 6.7.2
- Subject provides at least one primary PK parameter as defined in Section 12.5.3

- Subject ingests siremadlin or rineterkib at least 1 h before or 2 h after a meal (only applicable for treatment arm ruxolitinib + siremadlin or treatment arm ruxolitinib + rineterkib)
- Subject does not vomit within 4 hours after oral dosing of siremadlin, rineterkib or ruxolitinib (only applicable for treatment arm ruxolitinib + siremadlin or treatment arm ruxolitinib + rineterkib).
- Subject does not vomit within 2 hours after oral dosing of ruxolitinib (all other treatment arms).

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation (SD), median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, and by treatment group. This will include baseline JAK2V617F mutational status and review of Packed Red Blood Cell (PRBC) transfusion history for the last 12 weeks prior to baseline.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in days to ruxolitinib, siremadlin, crizanlizumab, sabatolimab, rineterkib, and NIS793 as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity will be summarized by means of descriptive statistics using the safety set.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system by treatment group.

The number of subjects with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons will be summarized by treatment group and all dosing data will be listed.

12.4 Analysis of the primary endpoint(s)

The primary objective of Part 1 of the study is to characterize the safety, tolerability, and the recommended Phase 2 dose (RP2D) of each combination partner used with ruxolitinib in subjects with myelofibrosis.

The primary objective of Parts 2 and 3 of the study is to evaluate the preliminary efficacy of the ruxolitinib combination treatments in subjects with myelofibrosis.

Due to permanent enrollment halt, the objectives for Parts 2 and 3 are no longer applicable.

12.4.1 Definition of primary endpoint(s)

Part 1

The primary endpoint in Part 1 is the incidence of dose-limiting toxicities (DLTs) within the first two treatment cycles.

Part 2 and Part 3 (Not applicable)

The primary endpoint in Parts 2 and 3 is the response rate (RR) at the end of Cycle 8 (for arms with NIS793) or Cycle 6 (all other arms).

The RR is the composite of anemia improvement and no spleen volume progression and no symptom worsening. For a subject to be considered a responder, all three components of the composite endpoint have to be fulfilled. The components of the composite endpoint are defined as follows:

- Anemia improvement is defined as an increase of hemoglobin from baseline of at least 1.5 g/dL. Anemia improvement requires absence of any PRBC transfusion in 12 weeks prior to achieving an increase of 1.5 g/dL. The increase in hemoglobin should be confirmed at least 2 weeks later.
- No spleen volume progression with progression defined as a spleen volume increase of 25% or more from baseline as measured by MRI/CT.
- No symptoms worsening as measured by the MFSAF version 4 patient reported outcome (PRO). An increase in total symptom score (TSS) of 10 or more from baseline is considered worsening of symptoms.

12.4.2 Statistical model, hypothesis, and method of analysis

12.4.2.1 Part 1

Identification of a recommended dose for siremadlin and rineterkib

Identification of the RP2D of the combination treatment will be based upon the estimation of the probability of DLT within the first two cycles for patients in the DDS. A recommended dose below the MTD may be identified based on other safety, clinical, PK, and PD data (Section 6.5.2). The dose escalation will be guided by a Bayesian analysis of dose-limiting toxicity (DLT) data from Cycle 1 and Cycle 2. The relationship between dose and the probability of DLT is modelled using logistic regression. Details of the model are given in Section 16.6.

Assessment of patient risk

After each cohort of patients that have been followed for two cycles, the BLRM will be updated and the posterior distribution for the risk of DLTs for patients at dose levels of siremadlin of interest will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of a DLT within the first two cycles lies within the following intervals:

Table 12-1 Toxicity levels

Under-dosing:	[0 , 0.16)
Targeted toxicity:	[0.16 , 0.33)
Excessive toxicity:	[0.33 , 1]

The escalation with overdose control (EWOC) principle

Dosing decisions are guided by the escalation with overdose control principal. A dose of the combination agent may only be used for newly enrolled patients if the risk of excessive toxicity at that dose is less than 25%.

Prior distributions

A meta-analytic-predictive (MAP) approach was used to derive the prior distribution for the model parameters. The MAP prior for the logistic model parameters for this study is the conditional distribution of the parameters given the historical data (see Neuenschwander et al 2014, Neuenschwander et al 2010, Spiegelhalter et al 2004). MAP priors are derived from hierarchical models, which take into account possible differences between the studies.

A full description of the application of the MAP approach to derive the prior distributions of the model parameters is given in Section 16.6.

Starting dose

The starting dose for siremadlin in combination with ruxolitinib is 20 mg (Section 6.5.1.1). For this dose the prior risk of excessive toxicity is 15.42% (see Section 16.6), which satisfies the EWOC criterion. Any dose lower than 20 mg also fulfills the EWOC criterion. A full assessment of the prior risk to patients is given in Section 16.6.

The starting dose for rineterkib in combination with ruxolitinib is 200 mg (Section 6.5.1.1). For this dose the prior risk of excessive toxicity is 18.85% (see Section 16.6), which satisfies the EWOC criterion. Any dose lower than 200 mg also fulfills the EWOC criterion. A full assessment of the prior risk to patients is given in Section 16.6.

Listing of DLTs

DLTs will be listed, and their incidence summarized by primary system organ class and worst grade (CTCAE version 5.0). Listings and summaries will be based on the DDS.

Identification of DLT probability for crizanlizumab, sabatolimab, and NIS793

For each combination treatment, the DLT probability is determined as the number of patients in the DDS who experienced a DLT divided by the number of patients in the DDS.

Any DLTs occurring will be listed, and their incidence summarized by primary system organ class and worst grade (CTCAE version 5.0). Listings and summaries will be based on the DDS.

12.4.2.2 Part 2 (Not applicable)

No formal hypothesis testing or between arm comparison will be conducted in Part 2. The objective of this part of the study is to explore the disease-modifying activity of the combination treatments, and to drop the arm(s) which lack promising activity.

The arms that will advance into Part 3 will be selected based on the totality of the data. That includes, among other data, efficacy, safety, PK/PD, [redacted] data as appropriate, and also data from the ruxolitinib single agent arm.

To determine whether a combination treatment has the potential to be disease-modifying and, as such, be eligible to advance into Part 3, the combination must not cross a specified futility boundary defined for the RR with respect to the primary composite endpoint.

A combination treatment arm that shows an early sign of outstanding efficacy by crossing a specific efficacy boundary (i.e. when at least 10 subjects of a combination treatment are evaluable) at the first interim look may expand into Part 3 seamlessly, without stopping at the second interim look.

At the second interim look, the combination treatment arm must not cross a specified futility boundary (i.e. when at least 25 subjects of a combination treatment are evaluable) defined for the RR with respect to the primary composite endpoint.

The threshold for the first interim look is shown in Table 12-2.

Table 12-2 1st interim look (seamless expansion to Part 3) efficacy threshold

Decision rule	Action
P (RR>0.3|D) > 80%	Preliminary efficacy declared

According to the first interim threshold, an arm is considered of clinical interest and will be advanced to Part 3 expansion if the posterior probability of the RR for the primary composite endpoint being greater than 0.3 is more than 80%. This first interim decision rule was determined such that arms with outstanding efficacy that warrant further development (i.e. True RR > 50%) will be advanced with higher probability, see Section 12.8.1.2 for details. Concerning the posterior probability of the RR, let i index the study arm, let p_i be the corresponding responder rate with respect to the primary endpoint, let n_i be the number of subjects of arm i, and let r_i be the number of responders in arm i. The number of responders r_i in arm i is modelled by a binomial distribution with parameters n_i and p_i. With the assumptions of a vague prior, *beta(1/2, 1/2)*, the posterior probability distribution of p_i is given by

$$p_i|n_i, r_i \sim beta\left(\frac{1}{2} + r_i, \frac{1}{2} + n_i - r_i\right)$$

For a given sample size n_i, the first interim threshold shown in Table 12-4 can be transformed into a number of responders with respect to the primary endpoints for which preliminary efficacy would be declared, as shown in Table 12-3.

Table 12-3 1st Interim look efficacy regions for a given sample size

n_i	Region
9	≥ 4
10	≥ 5
11	≥ 5
12	≥ 5

The futility threshold is shown in Table 12-4.

Table 12-4 Futility threshold

Decision rule	Action
P (RR≤0.2|D) > 50%	Declare combination arm futile

According to the futility threshold, an arm is dropped for futility if the posterior distribution of the RR for the primary composite endpoint is less than or equal to 0.2 with a probability of more than 50%. This futility decision rule was determined such that arms with a RR which are not of interest for further development, that are RRs of 10% or less, are likely to cross the futility threshold and would therefore be dropped at the end of Part 2, see Section 12.8.1.2 for details.

For a given sample size n_i, the futility threshold shown in Table 12-4 can be transformed into a number of responders with respect to the primary endpoints for which futility would be declared, see Table 12-5.

Table 12-5 Futility regions for a given sample size

n_i	Futility region
24	≤ 4
25	≤ 4
26	≤ 5
27	≤ 5

Due to the discrete nature of the binomial distribution, the futility region does not necessarily change in the sample size n_i.

12.4.2.3 Part 3 (Not applicable)

Part 3 of the study aims to further assess the efficacy of the combination by comparing them to ruxolitinib using the FAS.

The comparison of each combination arm with ruxolitinib will be performed separately based on a Bayesian model and include data from both Part 2 and Part 3.

In detail, let n_{rux} and r_{rux} be the sample size and the number of responders with respect to the primary composite endpoint in the ruxolitinib arm, respectively. Analogously, n_{comb} and r_{comb} denote the sample size and the number of responders in the combination arm to be compared with ruxolitinib. The number of responders within each arm is modelled by a binomial distribution with RR p_i (i = rux, comb). As in Section 12.4.2.2, a vague prior, *beta(1/2, 1/2)*, is assumed for p_i. This results in the beta-distributed posterior distribution for the RR, see Section 12.4.2.2. The study is considered to be successful with respect to the primary endpoint when the difference in RRs between combination arm and ruxolitinib arm is greater than zero with a probability of greater than or equal to 90%:

Figure 12-1 Success criterion for primary endpoint.

$$P(p_{comb} - p_{rux} > 0 | n_{rux}, r_{rux}, n_{comb}, r_{comb}) \geq 0.9$$

In addition to the comparison of the combination arm(s) with the ruxolitinib arm, the efficacy of the monotherapy of the agent combined with ruxolitinib will be evaluated in Part 3.

12.4.3 Handling of missing values/censoring/discontinuations

Subjects with missing assessments of hemoglobin, spleen volume or MF SAF TSS at the end of Cycle 8 (NIS793 arms) or Cycle 6 (all other arms) that prevent the evaluation of the primary endpoint will be considered non-responders to that treatment. Subjects who withdraw from treatment before assessment of hemoglobin, spleen volume or MF SAF TSS at the end of Cycle 8 (NIS793 arms) or Cycle 6 (all other arms) will be considered non-responders to that treatment as the primary endpoint cannot be evaluated for these subjects. Further details about visit windows considered when defining what constitutes a missing value will be provided in the SAP.

12.4.4 Sensitivity and Supportive analyses (Not applicable)

Sensitivity analyses

As sensitivity analyses, the primary endpoint will be evaluated with different prior distributions for the responder rates:

3. The prior distribution for the responder rate in the combination arm is the same prior as in the primary analysis, i.e., a vague prior. The prior distribution for the responder rate in the ruxolitinib arm is the robustified MAP prior based on historical data from INCB18424-351 (Comfort I) and CINC424A2352 (Comfort II). The detailed prior distribution will be specified in the SAP.
4. The prior distribution for the responder rate in the combination arm is obtained by updating the vague prior, *beta(1/2, 1/2),* using the number of responders from Part 1. The prior distribution for the responder rate in the ruxolitinib arm is not changed compared to the primary analysis. The detailed prior distribution will be specified in the SAP.

Supportive analyses

As supportive analyses, the definition of 'responders' will be changed compared to the primary endpoint by only considering the hemoglobin and spleen volume measurement. Thus, a subject is considered a responder if the following two criteria are fulfilled:

- Anemia improvement is defined as an increase of hemoglobin from baseline of at least 1.5 g/dL at the end of Cycle 8 (NIS793 arms) or Cycle 6 (all other arms) after randomization. Anemia improvement requires absence of any PRBC transfusion in the 12 weeks prior to achieving an increase of 1.5 g/dL and a confirmation of Hb increase at least 2 weeks later.
- No spleen volume progression is given when the spleen volume increase is smaller than 25% between baseline and the end of Cycle 8 (NIS793 arms) or Cycle 6 (all other arms) measured by MRI/CT.

12.5 Analysis of secondary endpoints

12.5.1 Efficacy [redacted] endpoint(s)

All secondary efficacy endpoint analyses will be analyzed using the Full Analysis Set (FAS).

12.5.1.1 Proportion of subjects achieving improvement of hemoglobin level (Not applicable)

Hemoglobin is measured at baseline and at least once per cycle. The change from baseline will be summarized by treatment group using descriptive statistics.

The proportion of subjects achieving improvement in hemoglobin ≥ 1.5 g/dL and ≥ 2.0 g/dL, respectively, from baseline to the end of Cycle 8 (NIS793 arms) or Cycle 6 (all other arms), and the end of Cycle 16 (NIS793 arms) or Cycle 12 (all other arms) will be estimated with 95% confidence intervals (Clopper-Pearson interval).

12.5.1.2 Change in spleen volume and spleen length

Spleen volume will be measured by MRI/CT at baseline, the end of Cycle 8 (NIS793 arms) or Cycle 6 (all other arms), the end of Cycle 16 (NIS793 arms) or Cycle 12 (all other arms) and at EOT (if not performed in the past 12 weeks) as noted in Table 8-6. The change from baseline will be summarized at each scheduled assessment time point during the core treatment phase using descriptive statistics.

The proportion of subjects with a spleen volume progression from baseline to the end of Cycle 8 (NIS793 arms) or Cycle 6 (all other arms) and the end of Cycle 16 (NIS793 arms) or Cycle 12 (all other arms) during the core treatment phase will be summarized descriptively. A spleen progression requires confirmation by MRI or CT showing a spleen volume increase of at least 25%.

The proportion of subjects achieving at least 25% and 35% reduction in spleen volume from Baseline to the end of Cycle 8 (NIS793 arms) or Cycle 6 (all other arms) and the end of Cycle 16 (NIS793 arms) or Cycle 12 (all other arms) during the core treatment phase as measured by MRI or by CT will be summarized descriptively.

Spleen length measurement will be conducted by manual palpation. Manual palpation will be performed on days 1 and 15 of cycles 1 to 3, and day 1 of subsequent cycles, as noted in the schedule of assessments in Table 8-3 and Table 8-5. The change from baseline at each planned scheduled point during the core treatment phase will be summarized using descriptive statistics.

The proportion of subjects who achieved at least 50% spleen length reduction at the end of Cycle 8 (NIS793 arms) or Cycle 6 (all other arms) from baseline during the core treatment phase for subjects with baseline splenomegaly that is palpable at greater than 10 cm, or became not palpable for subjects with baseline splenomegaly that is palpable at ≥5-≤10 cm will be estimated.

The proportion of subjects who achieved at least 50% spleen length reduction at the end of Cycle 4 (NIS793 arms) or Cycle 3 (all other arms) from baseline during the core treatment phase for subjects with baseline splenomegaly that is palpable at greater than 10 cm, or became not palpable for subjects with baseline splenomegaly that is palpable at ≥5-≤10 cm will be estimated.

The proportion of subjects who achieved at least 50% spleen length reduction at the end of Cycle 16 (NIS793 arms) or Cycle 12 (all other arms) from baseline during the core treatment phase for subjects with baseline splenomegaly that is palpable at greater than 10 cm, or became not palpable for subjects with baseline splenomegaly that is palpable at ≥5-≤10 cm will be estimated.

Spleen volume and spleen length data including change from baseline from both the core and extension treatment phases will be reported.

12.5.1.3 Change in symptoms assessed by MFSAF and EORTC

Symptoms of myelofibrosis will be measured by MFSAF v4.0 for the core treatment phase of the study.

The change from baseline in MFSAF total symptom score and individual symptoms will be summarized with descriptive statistics by cycle and treatment group. The proportion of subjects has no worsening in symptom at the end of Cycle 8 (NIS793 arms) or Cycle 6 (all other arms) and Cycle 16 (NIS793 arms) or Cycle 12 (all other arms) will be summarized. The symptom worsening is defined as an increase in TSS of 10 or more from baseline.

The proportion of subjects who achieved at least 50% reduction in MFSAF v4.0 Total Symptom Score (TSS) at the end of Cycle 4 (NIS793 arms) or Cycle 3 (all other arms), at the end of Cycle 8 (NIS793 arms) or Cycle 6 (all other arms) and at the end of Cycle 16 (NIS793 arms) or Cycle 12 (all other arms) respectively from baseline will be estimated.

Due to enrollment halt, EORTC data is not available for Parts 2 and 3 of the study. [redacted]

12.5.1.4 Progression free survival (Not applicable)

PFS is defined as the time from the date of randomization to the date of the first documented progressive splenomegaly, or accelerated phase, or deteriorating cytopenia, or leukemic transformation or death due to any cause (See Section 8.3.2.4).

PFS will be analyzed in the FAS population according to the randomized treatment group assigned at randomization. The PFS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group. The hazard ratio for PFS comparing a combination treatment with ruxolitinib single agent will be calculated, along with its 95% confidence interval, using a Cox model.

PFS will be censored if no PFS event is observed before the cut-off date or the date when a new anti-neoplastic therapy or another investigational treatment is started, whichever occurs earlier. The censoring date will be the date of last adequate assessment before either of these two dates.

12.5.1.5 Proportion of subjects achieving improvement in bone marrow fibrosis (Not applicable)

The grade of bone marrow fibrosis will be measured at baseline, the end of Cycle 8 (NIS793 arms) or Cycle 6 (all other arms), and every subsequent six cycles per Table 8-7. The grade of bone marrow fibrosis will be summarized descriptively for each scheduled point by treatment group. The proportion of patients achieving improvement in bone marrow fibrosis of ≥ 1 grade from baseline to the end of Cycle 8 (NIS793 arms) or Cycle 6 (all other arms), and the end of Cycle 16 (NIS793 arms) or Cycle 12 (all other arms) will be summarized.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used, except for summaries of DLTs, for which the DDS will be used in addition to the safety set. All listings and tables will be presented by treatment group. Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The overall observation period will be divided into three mutually exclusive segments:

1. **Pre-treatment period**: from day of subject's informed consent to the day before first dose of study treatment.
2. **On-treatment period**: from date of first dose of study treatment to 30 days after the date of the last administration of study treatment.
3. **On-extension treatment period**: from day of first dose of extension treatment to 30 days after the date of the last administration of study treatment.
4. **Post-treatment period**: starting at 31 days after the date of the last administration of study treatment.

In addition, the **overall safety period** is defined from date of first administration of study treatment to 30 days after the date of the last administration of ruxolitinib, siremadlin or rineterkib, 90 days after the date of the last administration of NIS793, or 105 days after the date of the last administration of crizanlizumab, or 150 days after the date of the last actual administration of sabatolimab, whichever is later.

Adverse events

All information obtained on adverse events will be displayed by treatment group for all subjects on Safety Set. Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period. The number (and percentage) of subjects with treatment emergent AEs will be summarized by primary system organ class, preferred term and maximum severity (based on CTCAE grades). Separate summaries will be provided for study medication related adverse events, deaths, serious adverse events, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment.

In addition, all AEs and SAEs which started during the overall safety period will be summarized.

A subject with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

All AEs, deaths and serious adverse events (including those from the pre, on-extension treatment period and post-treatment periods) will be listed and those started during the pre-treatment period, post-treatment period, and post-treatment/overall safety overlapping period will be flagged.

Vital signs

All vital signs data will be listed by treatment group, subject, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment group for core treatment phase.

12-lead ECG

All ECG data will be listed by treatment group, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment group for core treatment phase.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time for core treatment phase. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value for core treatment phase.

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE v5.0, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries will be generated separately for hematology, and biochemistry tests:

5. Listing of all laboratory data with values flagged to show the corresponding CTCAE v5.0 grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE v5.0:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each subject will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE v5.0 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE v5.0:

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

12.5.3 Pharmacokinetics

Pharmacokinetic parameters will be derived from the individual concentration versus time profile using a non-compartmental method as implemented in Phoenix WinNonlin (Pharsight, Mountain View, CA). The pharmacokinetic parameters described in Table 12-6 will be determined for each investigational drug, as deemed appropriate. Additional PK parameters may be estimated as needed.

Table 12-6 Non compartmental pharmacokinetic parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (Tlast)
AUCinf	The AUC from time zero extrapolated to infinity
AUC0-t	The AUC from zero to specified time points (amount x time x volume-1) for example 12, 24, 336 or 504h
Cmax	The maximum (peak) observed plasma drug concentration
Tlast	Time at which the last measurable concentration was observed (time)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
T1/2	The elimination half-life associated with the terminal slope (Lambda_z) of a semi logarithmic concentration-time curve
CL (CL/F)	The total body clearance (or apparent clearance) of drug from the plasma or serum
Vz (Vz/F)	The volume (or apparent volume) of distribution during terminal phase (associated with Lambda_z)
AR	Accumulation Ratio = AUC0-t (multiple Dose)/AUC0-t (single dose)

The PAS will be used in all pharmacokinetic data analysis and summary statistics Section 8.5.2.

Descriptive statistics of PK parameters for ruxolitinib, siremadlin, crizanlizumab, sabatolimab and rineterkib will be listed by treatment arm for PAS. Due to enrollment halt, PK parameters for NIS793 will be listed. Descriptive statistics will include arithmetic and geometric mean, median, SD, and coefficient of variance (CV), geometric CV, minimum and maximum. Zero concentrations will not be included in the geometric mean calculation. Since Tmax is generally evaluated by a nonparametric method, median values and ranges will be given for this parameter. The parameters that require terminal phase determination (AUCinf, T1/2, CL or CL/F and Vz or Vz/F) may not be adequately calculated by non-compartmental methods. All individual PK parameters will be listed using FAS. In Part 1, siremadlin PK data will be listed and summarized by dose level.

Plasma concentration data for ruxolitinib, siremadlin, crizanlizumab, sabatolimab, rineterkib and NIS793 will be listed by treatment arm for FAS. Descriptive summary statistics will be provided by treatment arm at each scheduled time point for PAS. Summary statistics will include n (number of subjects with non-missing values), mean (arithmetic and geometric), SD, CV% (arithmetic and geometric), median, minimum and maximum. Individual profiles with median by treatment as well as arithmetic mean with SD and geometric mean plasma concentration versus time profiles by treatment will be displayed graphically. Further graphical exploratory analyses will be carried out if deemed appropriate

12.5.3.1 Data handling principles

The subjects in the PAS will be used in the pharmacokinetic data analysis and PK summary statistics.

Bio-fluid concentrations will be expressed in mass per volume units. All Plasma concentration values below the limit of quantification (LLOQ) will be set to zero by the Bioanalyst, and will be displayed as zero in the listings and flagged. LLOQ values will be treated as zero in any calculations of summary statistics, and treated as missing for the calculation of the geometric means and their coefficient of variation (CV%). Any missing PK parameter or concentration will not be imputed.

12.5.3.2 Immunogenicity (only applicable to ruxolitinib combination arms with crizanlizumab, sabatolimab or NIS793) (Not applicable)

The presence and titer of anti-crizanlizumab, anti-sabatolimab antibodies, or anti-NIS793 (IG) will be listed by subject and summarized (when sample size is sufficient) using descriptive statistics to assess IG following one or more intravenous infusions of crizanlizumab, sabatolimab or NIS793.

[redacted]

[redacted]

[redacted]

[redacted]

12.7 Interim analyses (Not applicable)

No interim analysis is planned for Part 1. For the combination of ruxolitinib and siremadlin and ruxolitinib plus rineterkib, a BLRM will be used to assist assigning subjects to treatment dose levels, and to guide dose escalation decisions.

As the enrollment was permanently halted, the Part 2 has been prematurely discontinued with one randomized patient, and Part 3 will not be initiated, therefore the descriptions below for Parts 2 and 3 are not applicable.

In Part 2, two interim analyses are planned for each combination treatment arm. The first interim analysis will be conducted after at least 10 subjects of each combination treatment arm in Part 2 have completed Cycle 8 (arms with NIS793) or Cycle 6 (all other arms) or discontinued earlier. An arm that crosses the threshold for the first interim look and is considered safe, will be advanced to Part 3 seamlessly after enrollment of the arm in Part 2 (approximately 25 subjects) is completed, without stopping for the second interim look. The second interim analysis is planned after at least 25 subjects in each randomized arm have completed Cycle 8 (arms with NIS793) or Cycle 6 (all other arms) or discontinued earlier. As described in Section 3, in the second interim analysis, futile arms are dropped and not considered further for Part 3. The second interim analysis is not required if a combination treatment is advanced in Part 3 based on the first interim analysis. In Part 2, the criterion for the first interim look and the futility criterion are evaluated for each combination treatment arm based on the primary endpoint (Section 12.4.2.2) and no formal comparison between combination treatment arms and ruxolitinib will be performed.

In Part 3, no formal interim analysis is planned for this part of the trial. The first primary analysis will be performed once the first expanded Part 3 arms (combination treatment arm, compound monotherapy arm (ruxolitinib cessation arm), and monotherapy arm) have fully enrolled and have completed Cycle 8 (arms with NIS793) or Cycle 6 (all other arms) or discontinued earlier. Comparison of the primary endpoint between combination treatment arm(s) and ruxolitinib will be performed at the primary analysis with respect to the success criterion described in Section 12.4.2.3.

If the planned analyses are very close in time, multiple analyses will be performed at the same time to ensure timely operational feasibility for executing analyses and actions.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

12.8.1.1 Part 1

No formal statistical power calculations were performed to determine sample size for this part of the study.

Cohorts of 3 to 6 evaluable subjects will be enrolled in the dose escalation part including at least six subjects at the RP2D, as described in Section 6.5. Multiple cohorts may be sequentially enrolled to the same dose level. Additional cohorts of 1 to 6 subjects may be enrolled at any dose level below the estimated MTD for further elaboration of safety and pharmacokinetic parameters as required. At least 12 subjects are expected to be treated in the dose escalation part, for the model to have reasonable operating characteristics relating to its RP2D recommendation.

12.8.1.2 Part 2

The primary objective of Part 2 is to evaluate the preliminary efficacy of the combination treatments as outlined in Section 12.4.2.2. No formal hypothesis testing will be performed. While the totality of the data will be considered when deciding whether an arm will advance to

Part 3, the decision whether an arm showing preliminarily efficacy or is futile will be based on the posterior probability distribution for the responder rate within each arm.

Based on historical data from the COMFORT I and II studies, a primary endpoint RR of less than 10% is expected for the ruxolitinib single agent arm. A treatment with a true RR of

- less than 10% generally does not warrant further investigation,
- around 20% is potentially interesting,
- more than 30% is of interest.

Therefore, the criterion for the first interim look is defined as

$$P(p_i > 0.3|n_i, r_i) > 0.8$$

For a sample size of $n_i = 10$ with a vague prior distribution, *beta(1/2, 1/2)*, for the RR, an arm will be considered showing preliminary efficacy and advanced into Part 3 expansion seamlessly if ≥ 5 subjects are responders. Table 12-7 lists related operating characteristics for various true RRs.

Table 12-7 Probability of any arm to meet 1st interim look criterion for n = 10 and various true RRs

True RR	Single arm	Two arms	Four arms
0.35	0.2485	0.4352	0.6811
0.4	0.3669	0.5992	0.8393
0.45	0.4956	0.7456	0.9353
0.5	0.6230	0.8579	0.9798
0.55	0.7384	0.9316	0.9953
0.6	0.8338	0.9724	0.9992

The table indicates that with the planned sample size of $n_i = 10$, an arm with outstanding efficacy, i.e. a true RR of 0.5 or higher, has more than 60% probability to meet the criterion for the first interim look. If 2 arms each with true RR of 0.4, the probability of either arm meeting the criterion is close to 60%.

The futility decision will be guided by the criterion

$$P(p_i \leq 0.2|n_i, r_i) > 0.5$$

For a sample size of $n_i = 25$ with a vague prior distribution, *beta(1/2, 1/2)*, for the RR, an arm fulfills the futility criterion if ≤ 4 subjects are responders. Table 12-8 lists futility related operating characteristics for various true RRs.

Table 12-8 Probability of arm(s) to fulfill futility criterion for n = 25 and various true RRs

True RR	Probability of declaring futility for a single arm	Total probability of declaring futility for both arms when there are two arms in Part 2	Total probability of declaring futility for all 4 arms
0.05	0.9928	0.9857	0.9716
0.1	0.9020	0.8136	0.6620
0.15	0.6821	0.4653	0.2165
0.2	0.4207	0.1770	0.0313
0.25	0.2137	0.0457	0.0021
0.3	0.0905	0.0082	0.0001

The table shows that with the planned sample size of $n_i = 25$, an arm with low activity, i.e. a true RR of 0.1 or smaller, will fulfill the futility criterion with a probability of larger than 90%. For potentially interesting true RRs of $p_i = 0.2$, there is an approximately 40% chance that the arm fulfills the futility criterion. For arms with a true RR of more than 30%, the probability to fulfill the futility criterion is less than 10%. If two combination arms are advanced in Part 2 and both arms have low activity, i.e. the true RR of 0.1 or smaller, the overall probability that both arms are considered futile is larger than 80%. If four combination arms are advanced in Part 2 and all four arms have low activity, i.e. the true RR of 0.1 or smaller, the overall probability that all four arms are considered futile is approximately 66% or higher.

12.8.1.3 Part 3

Combination treatments not stopped for futility or safety after Part 2 will be considered for expansion into Part 3. After Part 3, each combination treatment will be compared to the ruxolitinib monotherapy arm by evaluating whether the difference in the posterior distributions of the RRs for the primary endpoint is larger than zero with a probability of 90%, i.e.

$$P(p_{comb} - p_{rux} > 0 | n_{rux}, r_{rux}, n_{comb}, r_{comb}) \geq 0.9$$

To determine the posterior distributions, data from both Part 2 and Part 3 is considered. In the following, the sample size considerations for the efficacy evaluation of one combination arm (combo) is illustrated. Table 12-9, Table 12-10 and Table 12-11 show the probability of possible outcomes for various true RRs in the ruxolitinib monotherapy arm (rux) for $n_{combo} = 45$ and $n_{rux} = 30$, 35 and 40 respectively, at the primary analysis (PA). Calculations assume the interim analysis (IA) is conducted with 25 subjects The four possible outcomes are based on the futility at interim analysis (Yes/No) and the treatment meet the success criterion at primary analysis (Yes/No). The first interim look boundary is in line with the second interim look boundary in respect of the require number of responders. In the first interim look, the arm can be expanded, when there are 5 or more responders out of 10 subjects. Similarly, the arm can be expanded

when there are 5 or more responders out of 25 subjects because the arm is not futile. In Table 12-9, assuming a true RR of 0.1 for ruxolitinib monotherapy, and a true RR of 0.35 for combination treatment, the probability that the primary analysis is successful when the interim is not futile, is 0.8933.

Table 12-9 Probability for each possible trial outcome of a combination treatment with N combo=45 and N rux=30

True RR for ruxolitinib monotherapy	True RR for combination treatment	IA Not Futile PA Fail	IA Not Futile PA Success	IA Futile PA Fail	IA Futile PA Success
0.05	0.05	0.0037	0.0035	0.9036	0.0893
	0.15	0.0678	0.2501	0.3800	0.3021
	0.2	0.0692	0.5101	0.1659	0.2547
	0.25	0.0467	0.7396	0.0568	0.1570
	0.3	0.0233	0.8863	0.0155	0.0750
0.1	0.1	0.0686	0.0294	0.8342	0.0678
	0.2	0.2328	0.3466	0.3025	0.1182
	0.25	0.2080	0.5783	0.1278	0.0860
	0.3	0.1400	0.7695	0.0435	0.0470
	0.35	0.0746	0.8933	0.0120	0.0201
0.15	0.15	0.2533	0.0646	0.6454	0.0367
	0.25	0.4143	0.3719	0.1759	0.0379
	0.3	0.3375	0.5720	0.0670	0.0235
	0.35	0.2214	0.7465	0.0208	0.0112
	0.4	0.1196	0.8709	0.0053	0.0042
0.2	0.2	0.4935	0.0858	0.4060	0.0146
	0.3	0.5442	0.3654	0.0808	0.0097
	0.35	0.4176	0.5504	0.0269	0.0052
	0.4	0.2709	0.7196	0.0073	0.0021
	0.45	0.1505	0.8472	0.0016	0.0007
Notes: IA = Interim Analysis; PA = Primary Analysis					

Table 12-10 Probability for each possible trial outcome of a combination treatment with N combo=45 and N rux=35

True RR for ruxolitinib monotherapy	True RR for combination treatment	IA Not Futile PA Fail	IA Not Futile PA Success	IA Futile PA Fail	IA Futile PA Success
0.05	0.05	0.0031	0.0041	0.9076	0.0853
	0.15	0.0576	0.2603	0.3446	0.3375
	0.2	0.0580	0.5214	0.1455	0.2752
	0.25	0.0375	0.7487	0.0489	0.1648
	0.3	0.0173	0.8922	0.0132	0.0773
0.1	0.1	0.0672	0.0308	0.8284	0.0736
	0.2	0.2227	0.3566	0.2969	0.1238
	0.25	0.1890	0.5972	0.1251	0.0886

	0.3	0.1174	0.7921	0.0421	0.0483
	0.35	0.0567	0.9113	0.0113	0.0207
0.15	0.15	0.2548	0.0631	0.6465	0.0356
	0.25	0.3955	0.3908	0.1768	0.0369
	0.3	0.3053	0.6042	0.0669	0.0235
	0.35	0.1883	0.7796	0.0205	0.0116
	0.4	0.0955	0.8951	0.0050	0.0044
0.2	0.2	0.4935	0.0858	0.4081	0.0125
	0.3	0.5190	0.3905	0.0811	0.0093
	0.35	0.3852	0.5827	0.0268	0.0052
	0.4	0.2403	0.7502	0.0072	0.0023
	0.45	0.1266	0.8711	0.0016	0.0008

Table 12-11 Probability for each possible trial outcome of a combination treatment with N combo=45 and N rux=40

True RR for ruxolitinib monotherapy	True RR for combination treatment	IA Not Futile PA Fail	IA Not Futile PA Success	IA Futile PA Fail	IA Futile PA Success
0.05	0.05	0.0027	0.0044	0.8851	0.1077
	0.15	0.0429	0.2750	0.3260	0.3561
	0.2	0.0386	0.5407	0.1281	0.2925
	0.25	0.0225	0.7637	0.0395	0.1743
	0.3	0.0096	0.9000	0.0097	0.0808
0.1	0.1	0.0631	0.0349	0.8277	0.0743
	0.2	0.1871	0.3923	0.2812	0.1395
	0.25	0.1522	0.6341	0.1134	0.1003
	0.3	0.0914	0.8182	0.0365	0.0540
	0.35	0.0425	0.9254	0.0094	0.0226
0.15	0.15	0.2447	0.0732	0.6434	0.0387
	0.25	0.3653	0.4209	0.1709	0.0428
	0.3	0.2760	0.6335	0.0636	0.0268
	0.35	0.1648	0.8032	0.0192	0.0129
	0.4	0.0796	0.9109	0.0047	0.0048
0.2	0.2	0.4860	0.0933	0.4066	0.0141
	0.3	0.5006	0.4089	0.0802	0.0103
	0.35	0.3626	0.6054	0.0264	0.0057
	0.4	0.2177	0.7729	0.0071	0.0024
	0.45	0.1085	0.8892	0.0015	0.0008

When the true RRs in the ruxolitinib monotherapy arm and the combination arm shown in Table 12-9, Table 12-10 and Table 12-11 are identical, the probabilities in the 'IA Not Futile PA Success' column can be considered to be the Bayesian equivalent to the type I error rate, i.e., the probability to wrongfully consider an inefficacious treatment as efficacious. This probability is smaller than 10% for all proposed sample sizes (ruxolitinib monotherapy sample size = 30, 35, 40), depending on the treatment arm and group. When the true RRs for the

ruxolitinib monotherapy arm is smaller than the combination arm, the probabilities in the 'IA Not Futile PA Success' column can be considered to be the Bayesian equivalent to the power. For a difference in RRs of 20%, the power is approximately 75% or higher for the considered ruxolitinib RRs for all proposed sample sizes.

Next, the probability that the difference between the posterior distributions of the RRs is calculated for several potential trial outcomes and it is illustrated for which outcomes the trial would be considered successful with respect to the primary endpoint. The outcomes are shown in Table 12-12 for $n_{combo} = 45$ and $n_{rux} = 30$, 35, and 40 respectively. The scenarios in which the trial would be considered successful are highlighted in bold.

Finally, Section 16.7 (Appendix 7) shows the simulated probabilities for a list of operating characteristic parameters under three hypothetical Part 2 and Part 3 study scenarios.

Table 12-12 Probability that the difference in the posterior distributions of the RRs is larger than zero

		Number of responders in ruxolitinib monotherapy arm n_{rux} = 30				
		3 (10.0%)	**5 (16.7%)**	**7 (23.3%)**	**9 (30.0%)**	**11 (36.7%)**
Number of responders in combination treatment arm n_{combo} = 45	**5(11.1%)**	0.5519	0.2420	0.0797	0.0206	0.0042
	7(15.6%)	0.7519	0.4432	0.1978	0.0683	0.0186
	9(20.0%)	0.8777	0.6368	0.3617	0.1602	0.0557
	11(24.4%)	**0.9456**	0.7881	0.5399	0.2953	0.1277
	13(28.9%)	**0.9780**	0.8888	0.7004	0.4560	0.2389
	15(33.3%)	**0.9919**	**0.9473**	0.8239	0.6167	0.3816
	17(37.8%)	**0.9973**	**0.9774**	**0.9066**	0.7549	0.5371
	19(42.2%)	**0.9992**	**0.9913**	**0.9554**	0.8583	0.6837
	21(46.7%)	**0.9998**	**0.9970**	**0.9809**	**0.9263**	0.8042
	23(51.1%)	**0.9999**	**0.9990**	**0.9927**	**0.9658**	0.8911
	25(55.6%)	**1.0000**	**0.9997**	**0.9975**	**0.9859**	**0.9461**
	27(60.0%)	**1.0000**	**0.9999**	**0.9993**	**0.9949**	**0.9765**
		Number of responders in ruxolitinib monotherapy arm n_{rux} = 35				
		3 (8.6%)	**5 (14.3%)**	**7 (20.0%)**	**9 (25.7%)**	**11 (31.4%)**
Number of responders in combination treatment arm n_{combo} = 45	**5(11.1%)**	0.6408	0.3327	0.1349	0.0443	0.0120
	7(15.6%)	0.8247	0.5586	0.3004	0.1301	0.0461
	9(20.0%)	**0.9247**	0.7456	0.4971	0.2709	0.1210
	11(24.4%)	**0.9710**	0.8706	0.6794	0.4462	0.2433
	13(28.9%)	**0.9899**	**0.9415**	0.8184	0.6219	0.4015
	15(33.3%)	**0.9968**	**0.9763**	**0.9083**	0.7688	0.5701
	17(37.8%)	**0.9991**	**0.9914**	**0.9587**	0.8737	0.7217
	19(42.2%)	**0.9998**	**0.9972**	**0.9835**	**0.9386**	0.8387
	21(46.7%)	**0.9999**	**0.9992**	**0.9941**	**0.9735**	**0.9167**
	23(51.1%)	**1.0000**	**0.9998**	**0.9981**	**0.9899**	**0.9620**
	25(55.6%)	**1.0000**	**1.0000**	**0.9995**	**0.9966**	**0.9848**
	27(60.0%)	**1.0000**	**1.0000**	**0.9999**	**0.9990**	**0.9947**
		Number of responders in ruxolitinib monotherapy arm n_{rux} = 40				
		3 (7.5%)	**5 (12.5%)**	**7 (17.5%)**	**9 (22.5%)**	**11 (27.5%)**

Number of responders in combination treatment arm n_{combo} = 45	**5(11.1%)**	0.7124	0.4200	0.1994	0.0786	0.0263
	7(15.6%)	0.8756	0.6546	0.4036	0.2068	0.0892
	9(20.0%)	**0.9531**	0.8235	0.6141	0.3884	0.2079
	11(24.4%)	**0.9842**	**0.9213**	0.7822	0.5823	0.3735
	13(28.9%)	**0.9952**	**0.9691**	0.8922	0.7482	0.5555
	15(33.3%)	**0.9987**	**0.9892**	**0.9530**	0.8661	0.7192
	17(37.8%)	**0.9997**	**0.9966**	**0.9819**	**0.9372**	0.8428
	19(42.2%)	**0.9999**	**0.9991**	**0.9938**	**0.9740**	**0.9223**
	21(46.7%)	**1.0000**	**0.9998**	**0.9981**	**0.9906**	**0.9662**
	23(51.1%)	**1.0000**	**1.0000**	**0.9995**	**0.9970**	**0.9872**
	25(55.6%)	**1.0000**	**1.0000**	**0.9999**	**0.9992**	**0.9958**
	27(60.0%)	**1.0000**	**1.0000**	**1.0000**	**0.9998**	**0.9988**

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Council on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written ICF, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.)

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. In addition, as the result of enrollment halt, a number of preplanned study objectives will not be pursued, the investigators were instructed not to continue to perform some of the study procedures to reduce the burden on ongoing patients. The assessments or visits not performed in the core treatment phase because of the permanent enrollment halt prior to implementation of the amended protocol version 08 will be summarized in the clinical study report.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request

Aaronson N. et Al (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology journal of National Cancer Institute, Vol. 85, No. 5 Marche 3. 1993 p. 365-76.

Abdel-Wahab OI, Levine RL (2009) Primary myelofibrosis: update on definition, pathogenesis, and treatment. Annu. Rev. Med. p. 233-45.

[redacted]

Akaike H (1974) A new look at the statistical model identification. Selected Papers of Hirotugu Akaike. Springer, New York, NY, p. 716-23.

Akhurst RJ, Hata A (2012) Targeting the TGFβ signalling pathway in disease. Nat Rev Drug Discov. p.790–812.

Anderson AC, Anderson DE, Bregoli L, et al (2007) Promotion of tissue inflammation by the immune receptor Tim-3 expressed on innate immune cells. Science p. 1141-3.

Arber DA, Orazi A, Hasserjian R, et al (2016) The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood p. 2391-405.

Asayama T, Tamura H, Ishibashi M, et al (2017) Functional expression of Tim-3 on blasts and clinical impact of its ligand galectin-9 in myelodysplastic syndromes. Oncotarget p. 88904-88917.

Ataga KI, Kutlar A, Kanter J, et al (2017) Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. N. Engl. J. Med. p. 429-39.

Babb J, Rogatko A, Zacks S (1998) Cancer phase I clinical trials: efficient dose escalation with overdose control. Stat Med p. 1103-20.

Barosi G, Mesa RA, Thiele J, et al (2008) Proposed criteria for the diagnosis of post-polycythemia vera and post-essential thrombocythemia myelofibrosis: a consensus statement from the International Working Group for Myelofibrosis Research and Treatment. Leukemia p. 437-38.

Berry SM, Connor JT, Lewis RJ (2015) The Platform Trial: An efficient strategy for evaluating multiple treatments. JAMA p. 1619-20.

Brahmer JR, Lacchetti C, Schneider BJ, et al (2018) Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J. Clin. Oncol. p. 1714-68.

[redacted]

Bullock AN, Fersht AR (2001) Rescuing the function of mutant p53. Nat. Rev. Cancer p. 68-76.

Cairo MS, Bishop M (2004) Tumour lysis syndrome: new therapeutic strategies and classification. Br. J. Haematol. p. 3-11.

Capdevila J, Cervantes A and Tabernero J (2012) New players in cancer therapeutics: focus on inhibitors of MDM2-p53 protein-protein interaction. Drugs of the Future p. 273-81.

Centurione L, Di Baldassarre A, Zingariello M, et al (2004) Increased and pathologic emperipolesis of neutrophils within megakaryocytes associated with marrow fibrosis in GATA-1(low) mice. Blood p. 3573-80.

Cervantes F (2014) How I treat myelofibrosis. Blood p. 2635-42.

Cervantes F, Correa JG, Hernandez-Boluda JC (2016) Alleviating anemia and thrombocytopenia in myelofibrosis patients. Expert Rev Hematol p. 489-96.

[redacted]

Chiba S, Baghdadi M, Akiba H, et al (2012) Tumor-infiltrating DCs suppress nucleic acid-mediated innate immune responses through interactions between the receptor TIM-3 and the alarmin HMGB1. Nat. Immunol. p. 832-42.

de Mingo Pulido Á, Gardner A, Hiebler S, et al (2018) TIM-3 Regulates CD103+ Dendritic Cell Function and Response to Chemotherapy in Breast Cancer. Cancer Cell p. 60-74.

Dempster AP, Laird NM, Rubin DB (1977) Maximum likelihood from incomplete data via the EM algorithm. Journal of the Royal Statistical Society, Series B p. 39(1):1-38.

Derynck R, Akhurst RJ (2007) Differentiation plasticity regulated by TGF-β family proteins in development and disease. Nature Cell Biol. p. 1000–1004.

Dueck A, Scherber R, Kosiorek H, et al (2017) Determining Meaningful Change in the Myelofibrosis Symptom Assessment Form (MFSAF) V2.0 using a Combination of Distribution- and Anchor-based Approaches in the COMFORT-I Trial. Madrid 22nd congress (June 22 -25, 2017).

Eischen CM, Lozano G (2009) p53 and MDM2: antagonists or partners in crime? Cancer Cell p. 161-62.

[redacted]

Frenette PS, Denis CV, Weiss L, et al (2000) P-Selectin glycoprotein ligand 1 (PSGL-1) is expressed on platelets and can mediate platelet-endothelial interactions in vivo. J. Exp. Med. p. 1413-22.

Gao X, Zhu Y, Li G, et al (2012) TIM-3 expression characterizes regulatory T cells in tumor tissues and is associated with lung cancer progression. PLoS ONE p. e30676.

Girish S, Martin SW, Peterson MC, et al (2011) AAPS workshop report: strategies to address therapeutic protein-drug interactions during clinical development. AAPS J p. 405-16.

[redacted]

Guy A, Gourdou-Latyszenok V, Le Lay N, et al (2019) Vascular endothelial cell expression of JAK2V617F is sufficient to promote a pro-thrombotic state due to increased P-selectin expression. Haematologica p. 70-81.

Gwaltney C, Paty J, Kwitkowski VE, et al (2017) Development of a harmonized patient-reported outcome questionnaire to assess myelofibrosis symptoms in clinical trials. Leuk. Res. p. 26-31.

Haanen J, Carbonnel F, Robert C, Kerr K, Peters S, Larkin J, Jordan K on behalf of the ESMO Guidelines Committee (2017) Management of toxicities from immunotherapy: ESMO clinical practive guidelines for diagnosis, treatment and follow-up. Annals of Oncology p. 119-142.

Huang SM, Zhao H, Lee JI, et al (2010) Therapeutic protein-drug interactions and implications for drug development. Clin. Pharmacol. Ther. p. 497-503.

Jan M, Chao MP, Cha AC, et al (2011) Prospective separation of normal and leukemic stem cells based on differential expression of TIM3, a human acute myeloid leukemia stem cell marker. Proc. Natl. Acad. Sci. U.S.A. p. 5009-14.

[redacted]

Joerger AC, Fersht AR (2008) Structural biology of the tumor suppressor p53. Annu. Rev. Biochem. p. 557-82.

Kikushige Y, Miyamoto T, Yuda J, et al (2015) A TIM-3/Gal-9 Autocrine Stimulatory Loop Drives Self-Renewal of Human Myeloid Leukemia Stem Cells and Leukemic Progression. Cell Stem Cell p. 341-52.

Kikushige Y, Shima T, Takayanagi S, et al (2010) TIM-3 is a promising target to selectively kill acute myeloid leukemia stem cells. Cell Stem Cell p. 708-17.

[redacted]

Lee JI, Zhang L, Men AY, et al (2010) CYP-mediated therapeutic protein-drug interactions: clinical findings, proposed mechanisms and regulatory implications. Clin Pharmacokinet p. 295-10.

Levine AJ, Oren M (2009) The first 30 years of p53: growing ever more complex. Nat. Rev. Cancer p. 749-58.

Martins CP, Brown-Swigart L, Evan GI (2006) Modeling the therapeutic efficacy of p53 restoration in tumors. Cell p. 1323-34.

[redacted]

Mascarenhas J, Lu M, Kosiorek H, Virtgaym E, Xia L, Sandy L, Mesa R, Petersen B, Farnoud N, Najfeld V, Rampal R, Dueck A, Hoffman R (2019) Oral idasanutlin in patients with polycythemia vera. Blood p. 525-533.

Mead AJ, Milojkovic D, Knapper S, et al (2015) Response to ruxolitinib in patients with intermediate-1-, intermediate-2-, and high-risk myelofibrosis: results of the UK ROBUST Trial. Br. J. Haematol. p. 29-39.

Mehta J, Wang H, Iqbal SU, et al (2014) Epidemiology of myeloproliferative neoplasms in the United States. Leuk. Lymphoma p. 595-600.

[redacted]

Mesa RA, Niblack J, Wadleigh M, et al (2007) The burden of fatigue and quality of life in myeloproliferative disorders (MPDs): an international Internet-based survey of 1179 MPD patients. Cancer p. 68-76.

Millard M, Pathania D, Grande F, et al (2011) Small-molecule inhibitors of p53-MDM2 interaction: the 2006-2010 update. Curr. Pharm. Des. p. 536-59.

Naymagon, L; Mascarenhas, J (2017) Myelofibrosis-Related Anemia. Current and Emerging Therapeutic Strategies. HemaSphere p. 1.

NCCN guidelines for specific populations available from: https: www nccn org/professionals/physician gls/defaults aspx#immunotherapy (Accessed 20 August 2020).

Ndhlovu LC, Lopez-Vergès S, Barbour JD, et al (2012) Tim-3 marks human natural killer cell maturation and suppresses cell-mediated cytotoxicity. Blood p. 3734-43.

Neuenschwander B, Branson M, Gsponer T (2008) Critical aspects of the Bayesian approach to phase I cancer trials. Stat Med p. 2420-39.

Neuenschwander B, Capkun-Niggli G, Branson M, et al (2010) Summarizing historical information on controls in clinical trials. Clin Trials p. 5-18.

Neuenschwander B, Matano A, Tang Z, et al (2014) A Bayesian Industry Approach to Phase I Combination Trials in Oncology. Statistical Methods in Drug Combination Studies p. 96 - 135.

[redacted]

Renfro LA, Mandrekar SJ (2018) Definitions and statistical properties of master protocols for personalized medicine in oncology. J Biopharm Stat p. 217-28.

Rollison DE, Howlader N, Smith MT, et al (2008) Epidemiology of myelodysplastic syndromes and chronic myeloproliferative disorders in the United States, 2001-2004, using data from the NAACCR and SEER programs. Blood p. 45-52.

Roth JA (2006) Adenovirus p53 gene therapy. Expert Opin. Biol. Ther., p. 55–61.

Saha MN, Qiu L, Chang H (2013) Targeting p53 by small molecules in hematological malignancies. J Hematol Oncol p. 23.

[redacted]

Saville BR, Berry SM (2016) Efficiencies of platform clinical trials: A vision of the future. Clin Trials p. 358-66.

Schmitt A, Drouin A, Masse JM, Guichard J, Shagraoui H, Cramer E (2002) Polymorphonuclear neutrophil and megakaryocyte mutual involvement in myelofibrosis pathogenesis . Leuk Lymphoma p. 719-724.

Schmitt A, Jouault H, Guichard J, et al (2000) Pathologic interaction between megakaryocytes and polymorphonuclear leukocytes in myelofibrosis. Blood p. 1342-47.

Shin DS, Ribas A (2015) The evolution of checkpoint blockade as a cancer therapy: what's here, what's next? Curr. Opin. Immunol. p. 23-35.

Shivdasani RA, Fujiwara Y, McDevitt MA, et al (1997) A lineage-selective knockout establishes the critical role of transcription factor GATA-1 in megakaryocyte growth and platelet development. EMBO J. p. 3965-73.

[redacted]

Spiegelhalter DJ, Abrams KR, Myles JP (2004) Bayesian Approaches to Clinical Trials and Health-Care Evaluation. Vol. 13. John Wiley & Sons.

[redacted]

[redacted]

Tefferi A, Barbui T (2019) Polycythemia vera and essential thrombocythemia: 2019 update on diagnosis, risk-stratification and management. Am. J. Hematol. p. 133-43.

Tefferi A, Cervantes F, Mesa R, et al (2013) Revised response criteria for myelofibrosis: International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) consensus report. Blood p. 1395-8.

Tefferi A, Vardiman JW (2008) Classification and diagnosis of myeloproliferative neoplasms: the 2008 World Health Organization criteria and point-of-care diagnostic algorithms. Leukemia p. 14-22.

Thiele J, Lorenzen J, Manich B, et al (1997) Apoptosis (programmed cell death) in idiopathic (primary) osteo-/myelofibrosis: naked nuclei in megakaryopoiesis reveal features of para-apoptosis. Acta Haematol. p. 137-43.

Valentino L, Pierre J (2006) JAK/STAT signal transduction: regulators and implication in hematological malignancies. Biochem. Pharmacol. p. 713-21.

Van Maerken T, Vandesompele J, Rihani A, et al (2009) Escape from p53-mediated tumor surveillance in neuroblastoma: switching off the p14(ARF)-MDM2-p53 axis. Cell Death Differ. p. 1563-72.

Vannucchi AM, Bianchi L, Cellai C, et al (2002) Development of myelofibrosis in mice genetically impaired for GATA-1 expression (GATA-1(low) mice). Blood p. 1123-32.

Vannucchi AM, Pancrazzi A, Guglielmelli P, et al (2005) Abnormalities of GATA-1 in megakaryocytes from patients with idiopathic myelofibrosis. Am. J. Pathol. p. 849-58.

Vannucchi AM , Bianchi L , Paoletti F , et al. (2005) A pathobiologic pathway linking thrombopoietin, GATA-1, and TGF-beta1 in the development of myelofibrosis . Blood p. 3493-3501.

Vassilev LT (2007) MDM2 inhibitors for cancer therapy. Trends Mol. Med. p. 23–31.

[redacted]

Ventura A, Kirsch DG, McLaughlin ME, et al (2007) Restoration of p53 function leads to tumour regression in vivo. Nature p. 661-5.

Ventz S, Alexander BM, Parmigiani G, et al (2017) Designing Clinical Trials That Accept New Arms: An Example in Metastatic Breast Cancer. J. Clin. Oncol. p. 3160-68.

Verstovsek S, Kantarjian H, Mesa RA, et al (2010) Safety and efficacy of INCB018424, a JAK1 and JAK2 inhibitor, in myelofibrosis. N. Engl. J. Med. p. 1117-27.

Verstovsek S, Talpaz M, Ritchie E, et al (2017) A phase I, open-label, dose-escalation, multicenter study of the JAK2 inhibitor NS-018 in patients with myelofibrosis. Leukemia p. 393-02.

Vogelstein B, Lane D, Levine AJ (2000) Surfing the p53 network. Nature p. 307-10.

Vogelstein B, Sur S, Prives C (2010) p53: the most frequently altered gene in human cancers. Nature Education p. 6.

Vyas P, Ault K, Jackson CW, et al (1999) Consequences of GATA-1 deficiency in megakaryocytes and platelets. Blood p. 2867-75.

Walton K, Johnson K, Harrison C (2017) Targeting TGF-β Mediated SMAD Signaling for the Prevention of Fibrosis. Front Pharmacol p. 1-11.

Wang JC , Chang TH , Goldberg A , et al (2006) Quantitative analysis of growth factor production in the mechanism of fibrosis in agnogenic myeloid metaplasia. Exp. Hematol. p. 1617-1623.

Woodcock J, LaVange LM (2017) Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. N. Engl. J. Med. p. 62-70.

[redacted]

Xiao G, Chicas A, Olivier M, et al (2000) A DNA damage signal is required for p53 to activate gadd45. Cancer Res. p. 1711-9.

Yan J, Zhang Y, Zhang JP, et al (2013) Tim-3 expression defines regulatory T cells in human tumors. PLoS ONE p. e58006.

Yang ZZ, Grote DM, Ziesmer SC, et al (2012) IL-12 upregulates TIM-3 expression and induces T cell exhaustion in patients with follicular B cell non-Hodgkin lymphoma. J. Clin. Invest. p. 1271-82.

Zhang Y, Ma CJ, Wang JM, et al (2011) Tim-3 negatively regulates IL-12 expression by monocytes in HCV infection. PLoS ONE p. e19664.

Zhang Y, Ma CJ, Wang JM, et al (2012) Tim-3 regulates pro- and anti-inflammatory cytokine expression in human CD14+ monocytes. J. Leukoc. Biol. p. 189-96.

Zhang Y, Xiong Y, Yarbrough WG (1998) ARF promotes MDM2 degradation and stabilizes p53: ARF-INK4a locus deletion impairs both the Rb and p53 tumor suppression pathways. Cell p. 725-34.

Zhou Q, Munger ME, Veenstra RG, et al (2011) Coexpression of Tim-3 and PD-1 identifies a CD8+ T-cell exhaustion phenotype in mice with disseminated acute myelogenous leukemia. Blood p. 4501-10.

[redacted]

16 Appendices

16.1 Appendix 1: Medications to be used with caution

Refer to Section 6.2.1.1 and in Table 16-1 below for guidance on cautionary use. For study treatment with siremadlin please refer to Section 6.2.1.1.1 for guidance on 'time window' to be applied.

Table 16-1 List of medications to be used with caution during study drug treatment

Mechanism of Interaction	Drug Names
Sensitive substrates of CYP3A (for patients on siremadlin or rineterkib)	abemaciclib, ABT-384, acalabrutinib, alisporivir, almorexant, aplaviroc, asunaprevir, avapritinib, AZD1305, BIRL 355, blonanserin, brecanavir, capravirine, eliglustat (in subjects CYP2D6 PM), entrectinib, L-771,688, terfenadine, ubrogepant, vilaprisan, zanubrutinib alpha-dihydroergocryptine, atorvastatin, avanafil, bosutinib, brotizolam, budesonide, buspirone, cobimetinib, danoprevir, darifenacin, dasatinib, ebastine, eletriptan, elvitegravir, eplerenone, everolimus, felodipine, fluticasone, grazoprevir, ibrutinib, ivabradine, ivacaftor, levomethadyl (LAAM), lomitapide, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, naloxegol, neratinib, nisoldipine, paritaprevir, perospirone, quetiapine, ridaforolimus, saquinavir, sildenafil, simeprevir, simvastatin, ticagrelor, tilidine, tipranavir, tolvaptan, triazolam, ulipristal, vardenafil, venetoclax, vicriviroc, voclosporin
Substrates of OATP1B1 (for patients on siremadlin)	aliskiren, ambrisentan, anacetrapib, atenolol, asunaprevir, atorvastatin, bromocriptine, caspofungin, celiprolol, danoprevir, digoxin, docetaxel, eliglustat, empagliflozin, ezetimibe, fimasartan, fexofenadine, fluvastatin, glyburide, maraviroc, methotrexate, rosuvastatin, saquinavir, simvastatin, paclitaxel, pitavastatin, pravastatin, repaglinide, rosuvastatin, simvastatin, valsartan, olmesartan, montelukast, ticlopidine, thyroxine
Substrates of MATE 1 (for patients on siremadlin)	acyclovir, ganciclovir, pindolol, pilsicainide, procainamide, ranitidine, topotecan, varenicline, Metformin, procainamide, glycopyrronium, cephalexin, cephadrine, fexofenadine, tetraethylammonium
Inhibitors of P-gp (for patients on siremadlin)	asian ginseng (Panax ginseng), asunaprevir, AZD5672, diosmin, five-flavor berry (Schisandra chinensis), flibanserin, glecaprevir/pibrentasvir, ivacaftor, maribavir, milk thistle (silymarin, silibinin)a, neratinib, osimertinib, pexidartinib, piperine, rifampin, rucaparib, sarecycline, sofosbuvir / velpatasvir / voxilaprevir, surfactant TPGS, tezacaftor / ivacaftor, valbenazine, vemurafenib, verapamil, zanubrutinib, alogliptin, amiodarone, azithromycin, canaglifozin, captopril, carvedilol, clopidrogel, cremophor EL and RH40, curcumin, daclatasvir, eliglustat, felodipine, fluvoxamine, fostamatinib, ginkgo (*Ginkgo biloba*)[a], green tea[a], ivacaftor, lapatinib, milk thistle (silymarin, silibinin)[a], mirabegron, nifedipine, nitrendipine, paroxetine, propafenone, quercetin, quinine, ranolazine, rolapitant, saquinavir , simeprevir, survorexant, talinolol, telmisartan, ticagrelor, tipranavir, tolvaptan, valspodar, vandetanib, velpatasvir, voclosporin, vorapaxar
Moderate inhibitors of CYP2C9	ataciguat, tienilic acid, oxandrolone, AZD1981, piperine, nitisinone, amiodarone, milk thistle (Silybum marianum)[a], phenylbutazone, azapropazone, bucolome, benzbromarone
Moderate inducers of CYP2C9	refer to footnote [b]
Moderate inhibitors of CYP2C8 (for patients on rineterkib)	deferasirox, letermovir, teriflunomide
Moderate inducers of CYP2C8 (for patients on rineterkib)	hormonal contraceptives, rifampin

Mechanism of Interaction	Drug Names
Proton pump inhibitors (PPIs) (for patients on rineterkib)	omeprazole, lansoprazole, dexlansoprazole, esomeprazole, pantoprazol, rabeprazole
Drugs which modify gastric pH (for patients on rineterkib)	[d]Antacids (e.g. TUMS®, Maalox®), [e]cimetidine, [e]famotidine, [e]nizatidine, [e]ranitidine
Drugs with known Torsade de Pointes risk[c] (for patients on rineterkib)	amiodarone, anagrelide, arsenic trioxide, astemizole (off US market), azithromycin, bepridil (off US market), chloroquine, chlorpromazine, cilostazol, ciprofloxacin, cisapride (off US market), citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone (not on US market), donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacin (removed from market), grepafloxacin (off market worldwide), halofantrine, haloperidol, ibogaine (only on non US market), ibutilide, levofloxacin, levomepromazine (only on non US market), levomethadyl (off US market), levosulpiride (only on non US market), mesoridazine (off US market), methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl (intra-coronary), pentamidine, pimozide, probucol (off US market), procainamide (oral off US market), propofol, quinidine, roxithromycin (only on non US market), sevoflurane, sotalol, sparfloxacin (off US market), sultopride (only on non US market), sulpiride (not on US market), terfenadine (off US market), terlipressin (only on non US market), terodiline (only on non US market), thioridazine, vandetanib.

[a] Herbal product

[b] Moderate inducers of CYP2C9 (reported as of April 2019 database search of University of Washington's Drug Interaction Database (druginteractioninfo.org)) listed as rifampin, enzalutamide, ritonavir and carbamazepine, are all excluded based on exclusion criteria as specified in Section 6.2.2 and Appendix 2, Table 16-2. Source: The list is adapted from the Novartis PK Sciences internal memorandum (v1, January, 2018): drug-drug interactions (DDI) database, which is compiled primarily from the Indiana University School of Medicine's "Clinically Relevant" Table (medicine.iupui.edu/flockhart/table.htm), the University of Washington's Drug Interaction Database (druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies" Note: Any drug mentioned in the above list should be contraindicated if they are excluded based on any other exclusion criteria as specified in Section 6.2.2 of the Study Protocol.
CYP: cytochrome P-450; OATP: organic-anion-transporting polypeptide

[c] Arizona Center for Education and Research on Therapeutics (CERT), Drugs that prolong the QT interval and/or induce Torsade de Pointes (wwwqtdrugs.org)

[d] Rineterkib should be administered at least 1 hour before or 2 hours after an antacid
[e] Rineterkib should be administered at least 3 hours before or 6 hours after an H2 receptor antagonist

16.2 Appendix 2: Prohibited medications

In general, the use of any concomitant medication deemed necessary for the care of the subject is permitted in this study, except as specifically prohibited in Section 6.2.2 and in Table 16-2 below. Refer to Section 6.2.2 for guidance on restrictions (including time window) to be applied during study drug treatment.

Table 16-2 List of prohibited medications during study drug treatment

Mechanism of Interaction	Drug Names
Narrow therapeutic index substrates of CYP3A[5] (for patients on siremadlin)	alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus
Strong inhibitors of CYP3A	ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak)[4], indinavir/ritonavir[4], tipranavir/ritonavir[4], ritonavir, cobicistat, indinavir, ketoconazole, troleandomycin, telaprevir, danoprevir/ritonavir[4], elvitegravir/ritonavir[4], saquinavir/ritonavir[4], lopinavir/ritonavir[4],

Mechanism of Interaction	Drug Names
	itraconazole, voriconazole, mibefradil, clarithromycin, posaconazole, telithromycin, grapefruit juice[3], conivaptan, nefazodone, nelfinavir, idelalisib, boceprevir, atazanavir/ritonavir[4], darunavir/ritonavir[4], ceritinib, LCL161, mifepristone, ribociclib, saquinavir
Moderate inhibitors of CYP3A (for patients on combination: siremadlin+ruxolitinib)	aprepitant, amprenavir, atazanavir, cimetidine, ciprofloxacin, crizotinib, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, faldaprevir, fluconazole, grapefruit juice[3], imatinib, isavuconazole, netupitant, nilotinib, tofisopam, *Schisandra sphenanthera* (nan wu wei zi)[1], asafoetida resin (*Ferula asafoetida*)[1], verapamil, duvelisib, fedratinib, letermovir, GSK2647544, lefamulin, casopitant, ravuconazole, istradefylline, ACT-178882, voxelotor, FK1706
Strong inducers of CYP3A	carbamazepine, enzalutamide, lumacaftor, phenobarbital, phenytoin, rifabutin, rifampicin, mitotane, St. John's wort (*Hypericum perforatum*)[1], avasimibe, rifapentine, apalutamide, ivosidenib
Moderate inducers of CYP3A (for patients on siremadlin)	bosentan, dabrafenib, efavirenz, etravirine, genistein2, modafinil, nafcillin, tipranavir/ritonavir, lopinavir, telotristat, thioridazine, semagacestat, cenobamate, lesinurad, rifabutin, lorlatinib, talviraline, daclatasvir and asunaprevir and beclabuvir, PF-06282999, elagolix, lersivirine
Strong inhibitors of CYP2C9	tasisulam, sulfaphenazole, miconazole
Strong inducers of CYP2C9	None reported[6]
Strong inhibitors of CYP2C8 (for patients on rineterkib)	gemfibrozil, clopidogrel
Strong inducers of CYP2C8 (for patients on rineterkib)	None reported[6]

[1] Herbal product
[2] Food product
[3] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g. low dose, single strength).
[4] Combination ritonavir-boosted regimens are listed here in the DDI memo as strong CYP3A inhibitors (to avoid potential confusion), even though some are considered moderate CYP3A inhibitors in the University of Washington's Drug Interaction Database.
[5] Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes)
[6] No drugs under this category have been reported as of June 2020 database search of University of Washington's Drug Interaction Database (druginteractioninfo.org).

Source: The list is adapted from the Novartis PK Sciences internal memorandum (v1, January, 2018): drug-drug interactions (DDI) database, which is compiled primarily from the Indiana University School of Medicine's "Clinically Relevant" Table (medicine.iupui.edu/flockhart/table.htm), the University of Washington's Drug Interaction Database (druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies". These lists are not comprehensive and are only meant to be used as a guide. Please contact the medical monitor with any questions. If a medication appears on both the list of prohibited and the list of medications to be used with caution, the medication is prohibited.

16.3 Appendix 3: MFSAF v4.0 PRO

Myelofibrosis Symptom Assessment Form version 4.0 7-Day Recall
(MFSAF v4.0 7-Day Recall)

Instructions: The following questions refer to symptoms that you may experience as a result of your myelofibrosis. Please read through and complete the questions on the following screens. There are no right or wrong answers. Please select the answer that best applies to you.

Items:

1. During the past 7 days, how severe was your worst fatigue (weariness, tiredness)?

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst Imaginable

2. During the past 7 days, how severe were your worst night sweats (or feeling hot or flushed)?

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst Imaginable

3. During the past 7 days, how severe was your worst itching?

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst Imaginable

4. During the past 7 days, how severe was your worst abdominal discomfort (feeling pressure or bloating)?

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst Imaginable

5. During the past 7 days, how severe was the worst pain under your ribs on your left side?

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst Imaginable

6. During the past 7 days, what was the worst feeling of fullness you had after beginning to eat?

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst Imaginable

7. During the past 7 days, how severe was your worst bone pain (not joint or arthritis pain)?

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst Imaginable

Myelofibrosis Symptom Assessment Form version 4.0 7-Day Recall (MFSAF v4.0 7-Day Recall)

16.4 Appendix 4: EORTC QLQ-C30 PRO

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _ _ _ _

Your birthdate (Day, Month, Year): _ _ _ _ _ _ _ _

Today's date (Day, Month, Year): 31 _ _ _ _ _ _ _ _

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

[redacted]

16.6 Appendix 6: Statistical considerations for dose-escalation

This appendix provides details of the statistical model, the derivation of prior distributions from historical data, the results of the Bayesian analyses and respective dosing decisions for some hypothetical data scenarios, and a simulation study of the operating characteristics of the model.

[redacted]

16.6.2 Statistical model

Let π(d) be the risk of DLT for the combination of ruxolitinib given at dose combination agent (siremadlin or rineterkib) dose d, the dose-DLT model is logistic:

Figure 16-1 Logistic DLT model.

$$\text{logit}\big(\pi(d)\big) = \log(\alpha) + \beta \log(d/d^*)$$

where d* is used to scale the doses. Hence, $\alpha>0$ is the odds of a DLT at d*; and $\beta>0$ is the increase in the log-odds of a DLT by a unit increase in log-dose.

16.6.3 Prior specifications for logistic parameters

The Bayesian approach requires the specification of prior distributions for the model parameters log(α) and log(β). A meta-analytic-predictive (MAP) approach was used to derive the prior distribution for these model parameters.

16.6.3.1 Description of the meta-analytic-predictive (MAP) approach

The aim of the MAP approach is to derive a prior distribution for the logistic parameters (log(α*), log(β*)) of the new trial using DLT data from historical studies.

Let r_{ds} and n_{ds} be the number of patients with a DLT, and the total number of patients at dose *d* in historical trial *s* (*s = 1,...,S*). The corresponding probability of a DLT is π_{ds}. The model specifications for the derivation of the MAP prior are as follows:

$$r_{ds} \mid \pi_{ds} \sim \text{Bin}(\pi_{ds}, n_{ds})$$

$$\text{logit}(\pi_{ds}) = \log(\alpha_s) + \beta_s \log(d/d^*)$$

$$\big(log(\alpha_s), log(\beta_s)\big) \mid \mu, \psi \sim \text{BVN}(\mu, \psi), \qquad s = 1, \dots, S$$

$$\big(log(\alpha^*), log(\beta^*)\big) \mid \mu, \psi \sim \text{BVN}(\mu, \psi)$$

The parameters $\mu = (\mu_1, \mu_2)$ and ψ are the mean and between-trial covariance matrix for the logistic parameters, the latter with standard deviations τ_1, τ_2, and correlation ρ. The parameters τ_1 and τ_2 quantify the degree of between trial heterogeneity. The following priors will be used for these parameters:

- normal priors for μ_1 and μ_2,
- log-normal priors for τ_1 and τ_2, and
- a uniform prior for ρ.

The MAP prior for single-agent model parameters in the new trial, $\big(log(\alpha^*), log(\beta^*)\big)$, is the predictive distribution

$$\big(log(\alpha^*), log(\beta^*)\big) \mid (r_{ds}, n_{ds} : s = 1, \dots, S)$$

Since the predictive distribution is not available analytically, MCMC is used to simulate values from this distribution. This is implemented using JAGS version 4.2.0. The sample from this distribution is then approximated by a mixture of bivariate normal (BVN) distributions. BVN mixtures with increasing numbers of mixture components are fitted to the sample using the expectation-maximization (EM) algorithm (Dempster et al 1977). The optimal number of components of the mixture is then identified using the Akaike information criterion (AIC) (Akaike H 1974).

16.6.3.2 Single-agent siremadlin

For the MAP model for siremadlin, reference dose $d^* = 50$ mg is used, and data from one historical study with four regimens is available, so $S = 4$ is chosen.

Weakly informative normal priors are assumed for μ_1 and μ_2, with means corresponding to a risk of DLT at the reference dose of 1/3, and a doubling in dose leading to a doubling in the odds of the risk of a DLT, respectively. Priors for τ_1 and τ_2 are assigned such that (1) their medians correspond to substantial between trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations (Neuenschwander et al 2014).

The prior distributions for the model used for deriving the MAP priors are specified in Table 16-3.

Table 16-3 Prior distributions for the parameters of the MAP model used to derive the prior for the single-agent model parameters

Parameter	Prior Distribution
μ_1	N (mean = logit (1/3), sd = 2)
μ_2	N (mean = 0, sd = 1)
τ_1	log-normal (mean = log (0.5), sd = log (2)/1.96)
τ_2	log-normal (mean = log (0.25), sd = log (2)/1.96)
ρ	uniform (-1,1)

Historical data from study CHDM201X2101

The prior is determined based on solid tumor data from study CHDM201X2101.

In this study, four different regimens and dose-schedules where studied:

- 1A: dose on day 1 of a three week cycle
- 1B: dose on day 1 and on day 8 of a four week cycle
- 2A: once dose daily for the first two weeks of a four week cycle
- 2C: once daily dosing for the first week of a four week cycle

The doses in the difference regimens are scaled to fit the schedule of siremadlin in the combination study, which is once daily for the first five days in a four-week cycle.

In study CHDM201X2101, the original interest was in DLTs in cycle 1, however after observing cumulative toxicity DLTs within the first two cycles were considered for the recommended dose for expansion (document release date 28-Oct-2016). As the ruxolitinib combination study focuses on DLTs occurring in the first two cycles, the corresponding DLTs from the study CHDM201X2101 were considered. When building the MAP prior distribution for siremadlin, the different regimens from study CHDM201X2101 were considered as different studies.

Table 16-4 Regimens and doses from study CHDM201X2101

Regimen	Dose level	Dose per cycle	Dose per day in 5 day schedule	N	DLTs (Cycle 1)	HEM DLTs (Cycle 2)	DLTs considered for MAP
1A	12.5	12.5	2.5	1	0	0	0
	25	25	5.0	1	0	0	0
	50	50	10.0	4	0	1	1
	100	100	20.0	4	0	0	0
	200	200	40.0	5	0	1	1
	250	250	50.0	6	0	1	1
	350	350	70.0	5	2	2	4
1B	120	240	48.0	9	0	2	2
	150	300	60.0	8	1	1	2
	200	400	80.0	3	0	Data n/a at cutoff	0
2A	1	14	2.8	1	0	0	0
	2	28	5.6	2	0	0	0
	4	56	11.2	4	0	0	0
	7.5	105	21.0	4	0	0	0
	15	210	42.0	4	0	1	1
	20	280	56.0	5	0	4	4
2C	15	105	21.0	8	0	1	1
	20	140	28.0	6	0	0	0
	25	175	35.0	5	2	0	2

Summary of prior distributions for siremadlin

To obtain the MAP prior for (log(α), log(β)), the predictive distribution obtained from data in Table 16-4 will be mixed with a vague prior assuming a weight of 0.5. This mixing takes into account the fact the that patient population from study CHDM201X2101 and this combination study are not identical and that in this combination study a single-agent model is used to account for both the effect of siremadlin and potential interaction with ruxolitinib.

The MAP prior for (log(α), log(β)) is a mixture of three multivariate normal distributions and it is summarized in Table 16-5.

Table 16-5 Prior distribution for the siremadlin model parameters

Prior for (log(α), log(β)) in the single agent DLT-model for the combination of siremadlin and ruxolitinib				
	Mean	**Standard Deviations**	**Correlation**	**Weight**
MAP component 1	(-0.771 ,0.492)	(0.700, 0.435)	0.221	0.3255
MAP component 2	(-0.884, 0.051)	(0.573, 0.643)	0.237	0.1745
MAP component 3	(logit(1/3), 0)	(2, 1)	0	0.5
Prior summaries for DLT rates for are summarized in Table 16-6.				

Table 16-6 Summary of prior distribution of DLT rates for the combination of siremadlin and ruxolitinib

Siremadlin Dose (mg)	Prior Probabilities that P(DLT) is in the interval:			Mean	SD	Quantiles		
	(0, 0.16)	(0.16, 0.33)	[0.33,1]			2.5%	50%	97.5%
10	0.7982	0.0967	0.1051	0.1191	0.1895	0.0001	0.0443	0.7679
20	0.6526	0.1932	0.1542	0.1793	0.2103	0.0011	0.1046	0.8384
30	0.4687	0.3077	0.2235	0.2392	0.2217	0.0050	0.1713	0.8792
40	0.3035	0.3630	0.3335	0.2996	0.2297	0.0110	0.2425	0.9087

16.6.3.3 Single-agent rineterkib

For the MAP model for rineterkib, reference dose $d^* = 300$ mg is used, and data from $S = 1$ historical studies (First in Human study) is available.

Weakly informative normal priors are assumed for μ_1 and μ_2, with means corresponding to a 10% risk of DLT at the reference dose of 300 mg, and a doubling in dose leading to a doubling in the odds of the risk of a DLT, respectively. Priors for τ_1 and τ_2 are assigned such that (1) their medians correspond to substantial between trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations (Neuenschwander et al 2014).

The prior distributions for the model used for deriving the MAP priors are specified in Table 16-7.

Table 16-7 Prior distributions for the parameters of the MAP model used to derive the prior for the rineterkib model parameters

Parameter	Prior Distribution
μ_1	N (mean = logit (0.1), sd = 2)
μ_2	N (mean = 0, sd = 1)
τ_1	log-normal (mean = log (0.5), sd = log (2)/1.96)
τ_2	log-normal (mean = log (0.25), sd = log (2)/1.96)
ρ	uniform (-1,1)

Historical data from Study LTT462X2101

The dose-DLT data from rineterkib single agent from study LTT462X2101 are considered as the relevant information (Table 16-8) and used to derive the prior distribution for the BLRM parameters (log(α), log(β)). The clinical study LTT462X2101 is a phase I dose finding study of oral rineterkib in adult patients with advanced solid tumors harboring MAPK pathway alterations.

The DLT observation window in the Phase I dose escalation part of this trial was 4 weeks. A review of AE records of the patients did not indicate any significant additional toxicity in the 2nd cycle of treatment, suggesting data from the 1 cycle DLT evaluation period of study LTT462X2101 is also informative for a 2 cycle DLT evaluation period.

Table 16-8 Historical DLT data from Study LTT462X2101

Dose (mg, daily/QD)	Number of patients	Number of DLTs
45	2	0
100	3	0
150	6	1
200	4	1
300	7	0
400	4	0
450	7	2
600	3	3

Summary of prior distributions for rineterkib

To obtain the MAP prior for (log(α), log(β)), the predictive distribution obtained from data in Table 16-9 will be mixed with a vague prior assuming a weight of 0.5. This mixing takes into account the fact the that patient population from study LTT462X2101 and this combination study are not identical and that in this combination study a single-agent model is used to account for both the effect of rineterkib and potential interaction with ruxolitinib.

The MAP prior for (log(α), log(β)) is a mixture of four multivariate normal distributions and it is summarized in Table 16-9.

Table 16-9 Prior distribution for the model parameters

Prior for (log(α), log(β)) in the single agent DLT-model for the combination of siremadlin and ruxolitinib				
	Mean	**Standard Deviations**	**Correlation**	**Weight**
MAP component 1	(-1.737, 0.330)	(1.135, 0.685)	-0.089	0.190
MAP component 2	(-1.518, 0.571)	(0.648, 0.478)	-0.289	0.163
MAP component 3	(-1.491, -0.211)	(0.764, 0.868)	-0.018	0.147
MAP component 4	(logit(1/4), 0)	(2, 1)	0	0.5

Prior summaries for DLT rates for are summarized in Table 16-10.

Table 16-10 Summary of prior distribution of DLT rates for the combination of rineterkib and ruxolitinib

Rineterkib Dose (mg)	**Prior Probabilities that P(DLT) is in the interval:**			**Mean**	**SD**	**Quantiles**		
	(0, 0.16)	**(0.16, 0.33)**	**[0.33,1]**			**2.5%**	**50%**	**97.5%**
100	0.7673	0.1171	0.1155	0.1273	0.1905	0.0002	0.0492	0.7552
200	0.6126	0.1989	0.1885	0.1966	0.2183	0.0040	0.1142	0.8444
300	0.4217	0.2923	0.2860	0.2705	0.2378	0.0114	0.1934	0.8999

16.6.4 Hypothetical on-study data scenarios

To illustrate the performance of the Bayesian model used to guide dose escalation, hypothetical dose escalations scenarios following the provisional dose levels specified in Section 6.5.1 are displayed. In each case, the maximum dose that can be used in the next cohort of subjects is shown. This recommended Phase 2 dose is determined using the model-based assessment of

the risk of DLT in future subjects and the dose escalation rules as described in Section 6.5.1. In practice, a dose below the maximum might be chosen based on additional safety, PK or PD information (Section 6.5).

16.6.4.1 Scenarios for siremadlin

The first three hypothetical dose escalation scenarios in Table 16-11 are for the case that the first cohort contains six subjects being administered a combination treatment with a siremadlin dose of 20 mg. Scenarios 4, 5, 6 and 7 are for the second cohort and the case that the first cohort contains six subjects receiving 20 mg siremadlin and two subjects having DLTs. Scenarios 8 and 9 demonstrate if enrolling 2 and 3 subjects in Arm 1, the first 2 subjects experience a DLT, then further enrollment into Arm 1 will stop and the combination treatment will not open in Part 2.

Table 16-11 Hypothetical dose escalation scenarios for a cohort size of n=6 subjects receiving a dose of 20 mg siremadlin

Scenario	Siremadlin Dose [mg]	Number of		Possible next dose levels		
		patients	DLTs	Dose [mg]	Median P(DLT)	P(excessive toxicity)
1	20	6	0	40	0.162	0.122
2	20	6	1	30	0.192	0.148
3	20	6	2	20	0.206	0.219
4	20	6	2			
	20	3	0	30	0.233	0.222
5	20	6	2			
	20	4	0	30	0.221	0.183
6	20	6	2			
	20	5	0	30	0.212	0.159
7	20	6	2			
	20	3	1	20	0.233	0.247
8	20	2	2	10*	0.554	0.696
9	20	3	2	10*	0.275	0.435
*The possible next dose level is not available, as the probability of excessive toxicity of the lower dose does not satisfy EWOC criteria. The combination treatment will not open in Part 2.						

16.6.4.2 Scenarios for rineterkib

The first three hypothetical dose escalation scenarios in Table 16-12 are for the case that the first cohort contains six subjects being administered a combination treatment with a rineterkib dose of 200 mg. Scenarios 4, 5, 6 and 7 are for the second cohort and the case that the first cohort contains six subjects receiving 200 mg rineterkib and different number of subjects having DLTs. Scenarios 8 and 9 demonstrate if enrolling 2 and 3 subjects in the rineterkib Arm (Arm 4), the first 2 subjects experience a DLT, then further enrollment into the rineterkib Arm will stop and the combination treatment will not open in Part 2.

Table 16-12 Hypothetical dose escalation scenarios for a cohort size of n=6 subjects receiving a dose of 200 mg rineterkib

Scenario	RineterkibDose [mg]	Number of		Possible next dose levels		
		patients	DLTs	Dose [mg]	Median P(DLT)	P(excessive toxicity)
1	200	6	0	300	0.108	0.064
2	200	6	1	300	0.203	0.204
3	200	6	2	100	0.119	0.100
4	200	6	0			
	300	6	2	300	0.192	0.124
5	200	6	1			
	300	6	1	300	0.186	0.099
6	200	6	1			
	300	6	2	200	0.160	0.070
7	200	6	2			
	100	3	0	200	0.188	0.157
8	200	2	2	100*	0.493	0.656
9	200	3	2	100*	0.268	0.418
*The possible next dose level is not available, as the probability of excessive toxicity of the lower dose does not satisfy EWOC criteria. The combination treatment will not open in Part 2.						

16.7 Appendix 7: Simulation for hypothetical Part 2 and Part 3 study scenarios (Not applicable)

The simulation assumed three groups for Part 2 and Part 3 of the study. Group 1 included Combination 1, Combination 2 and Ruxolitinib monotherapy; Group 2 included Combination 3, Combination 4 and Ruxolitinib monotherapy; Group 3 included Combination 5 and Ruxolitinib monotherapy. The three groups are assumed to be enrolled in a sequential manner within Part 2 and Part 3. Three scenarios are simulated with the true RR for each treatment arm shown in Table 16-13. The probabilities for a list of operating characteristic parameters for the three hypothetical scenarios are presented in Table 16-14.

Table 16-13 Hypothetical true RR for each treatment arm

Scenarios	True RR					
	RUX	COMB1	COMB2	COMB3	COMB4	COMB5
Scenario1	0.05	0.05	0.05	0.05	0.05	0.05
Scenario2	0.05	0.3	0.05	0.05	0.05	0.05
Scenario3	0.05	0.05	0.2	0.3	0.05	0.25

Table 16-14 Probabilities for a list of operating characteristic parameters for hypothetical scenarios of the study

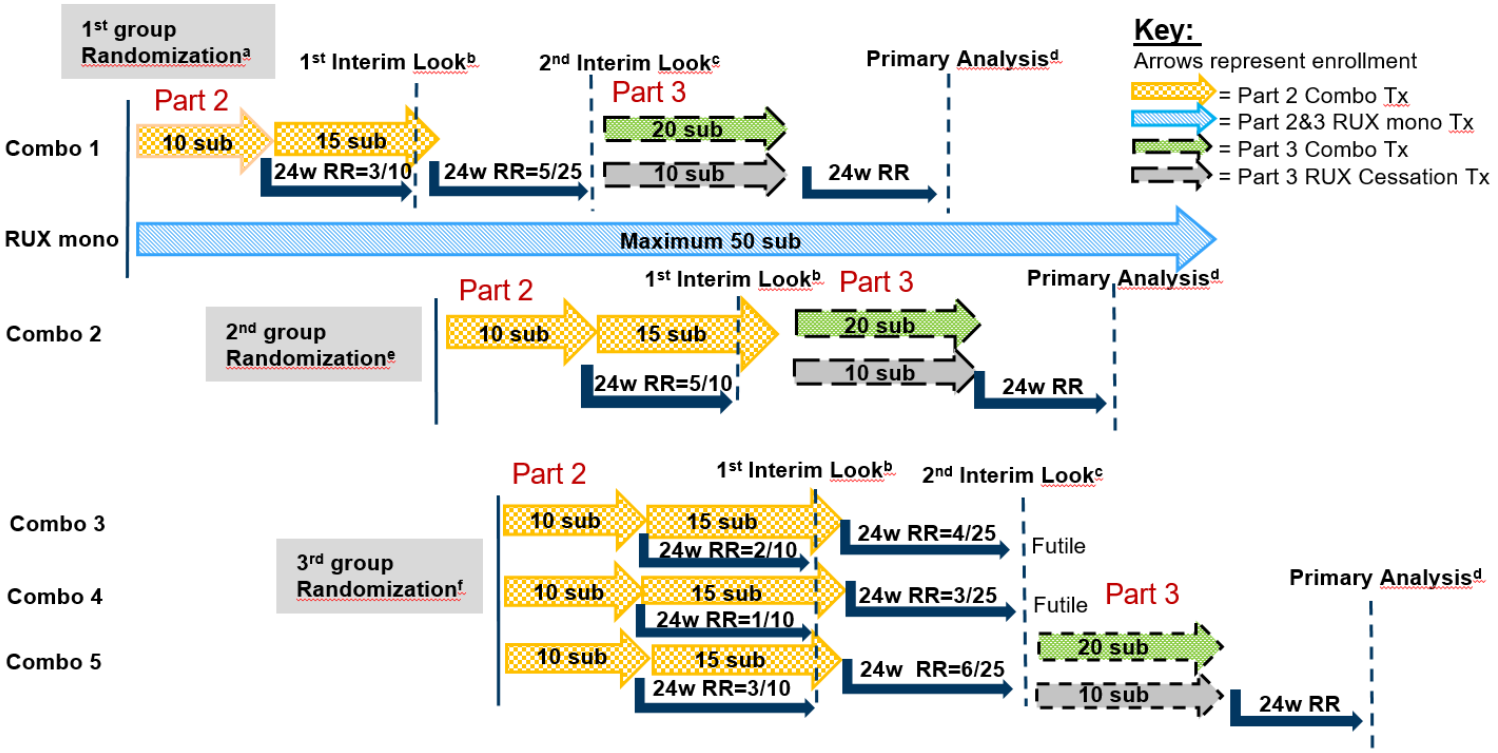
Scenarios	Probabilities			
	All combo arms are futile	All combo arms are futile at IA or not success at PA	Any combo arm(s) is not futile at IA and success at PA	Any combo arm(s) with true RR>0.2 is not futile at IA and success at PA
Scenario1	0.9651	0.9800	0.0200	0.0000
Scenario2	0.0894	0.1145	0.8855	0.8841
Scenario3	0.0100	0.0177	0.9823	0.9713

Scenario 1 assumed all treatment arms have equal true RR and do not warrant further development (RR=0.05). The column 'All combo arms are futile at IA or not success at PA' in Table 16-14 shows the probability to reject all inefficacious treatments at interim or primary analysis. Scenario 2 assumed one combination treatment in Group 1 has a true RR of interest (i.e. RR>0.2). Scenario 3 assumed one combination treatment in each Group has true RR of interest (i.e. RR>0.2). The column 'Any combo arm(s) with true RR>0.2 is not futile at IA and success at PA' shows the probability to select any combination arm or arms that are of interest for the study.

16.8 Appendix 8: Hypothetical example to illustrate Part 2 and Part 3 study design (Not applicable)

A hypothetical example below in Figure 16-2 aims to illustrate the randomization parts of the study design. Part 1 is not included in the diagram. The number of groups and the combination treatment arm(s) within each group are hypothetical. A ruxolitinib monotherapy arm is open in group 1 and remains open as additional groups start enrollment. In Figure 16-2, the results of the primary endpoint, i.e. Response Rate (RR), are assumed to illustrate possible actions at the 1st interim look and 2nd interim look.

Figure 16-2 Hypothetical example for Part 2 and Part 3 study design



a. Group 1: Part 2 randomization started with Combo 1 (combination treatment 1) and RUX mono (ruxolitinib monotherapy control). Combo 1 meets criteria at 2nd interim analysis to expand enrollment to this arm in Part 3.
b. The 1st Interim look will take place when the first 10 subjects of a combination treatment arm have completed 24 weeks of treatment. In the case of outstanding efficacy, the combination treatment arm may expand for seamless enrollment to Part 3. e.g. Outstanding efficacy boundary ≥5 responders out of 10 subjects (RR≥5/10).
c. The 2nd Interim look will take place when the first 25 subjects of a combination treatment arm have completed 24 weeks of treatment. In the case of futility, further enrollment in the arm will be dropped from Part 3, e.g. Futility boundary ≤4 responders/25 subjects (RR≤4/25). Otherwise, further enrollment in the arm will be expanded in Part 3.
d. The final look (Primary Analysis) for each arm will take place when 45 subjects have completed 24 weeks of treatment.
e. Group 2: Combo 2 started randomization with other open arms after Part 1 safety evaluation. Combo 2 seamlessly expanded to Part 3 based on results of the 1st interim analysis (RR=5/10).
f. Group 3: Combo 3, Combo 4, and Combo 5 started randomization with other open arms after Part 1 safety evaluation. Combo 3 and Combo 4 completed Part 2 and declared futile at the 2nd interim analysis and not expand in Part 3 (RR=4/25 and RR=3/25, respectively). Combo 5 expanded to Part 3 after the 2nd interim analysis (RR=6/25).

If the planned analyses are very close in time, multiple analyses will be performed at the same time to ensure timely operational feasibility for executing analyses and actions.

Notes:
The figure is not drawn for scale
Combo/Combo Tx = combination treatment
RUX mono = ruxolitinib monotherapy treatment
Sub = subject(s)