morphosys	**SAP Approval**
Number of Pages	Page **1** of **1**

Clinical Trial Title	A Phase 1/2 Study of CPI-0610, a Small Molecule Inhibitor of BET Proteins: Phase 1 (Dose Escalation of CPI-0610 in Patients with Hematological Malignancies) and Phase 2 (Dose Expansion of CPI-0610 with and without Ruxolitinib in Patients with Myeloproliferative Neoplasms).
Clinical Trial Protocol Number	CPI 0610-02 / NCT02158858
SAP	V7.0
Version Date	19-FEB-2025

I hereby approve the Statistical Analysis Plan

Remove signature fields for Clinical Pharmacology Scientist and Clinical Biomarker Lead, if not applicable

Signatures	
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Statistical Analysis Plan of Study CPI 0610-02 (MANIFEST)

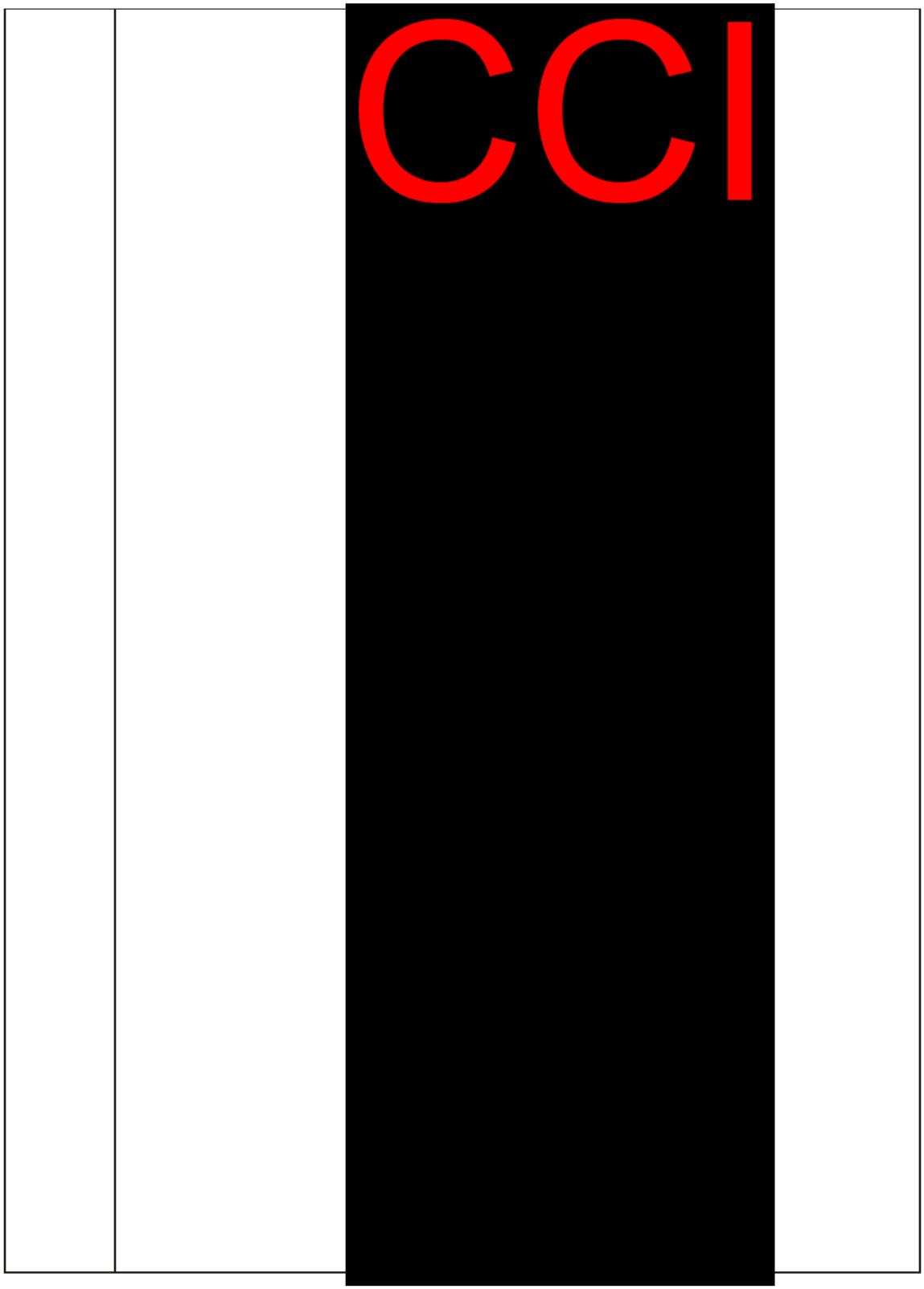
Protocol Number	CPI 0610-02
Protocol Title	A Phase 1/2 Study of CPI-0610, a Small Molecule Inhibitor of BET Proteins: Phase 1 (Dose Escalation of CPI-0610 in Patients with Hematological Malignancies) and Phase 2 (Dose Expansion of CPI-0610 with and without Ruxolitinib in Patients with Myeloproliferative Neoplasms).
Sponsor	Constellation Pharmaceuticals Inc., (Constellation Pharmaceuticals, Inc. is a fully owned subsidiary of MorphoSys Inc.) 470 Atlantic Avenue, FL14 Boston, MA, 02210 USA
IND Number	147351
EudraCT Number	2018-000579-34
Author	PPD
Date	19 Feb 2025
SAP Version	7.0

1 Table of Contents

1 Document history

Document History – Changes compared to the previous finalized version.

Version	Date	Changes	Rationale for Change
v1.0	13 JULY 2022-	Original	Not applicable
V1.1	18 NOVEMBER 2022	CCI	Updates to v1.0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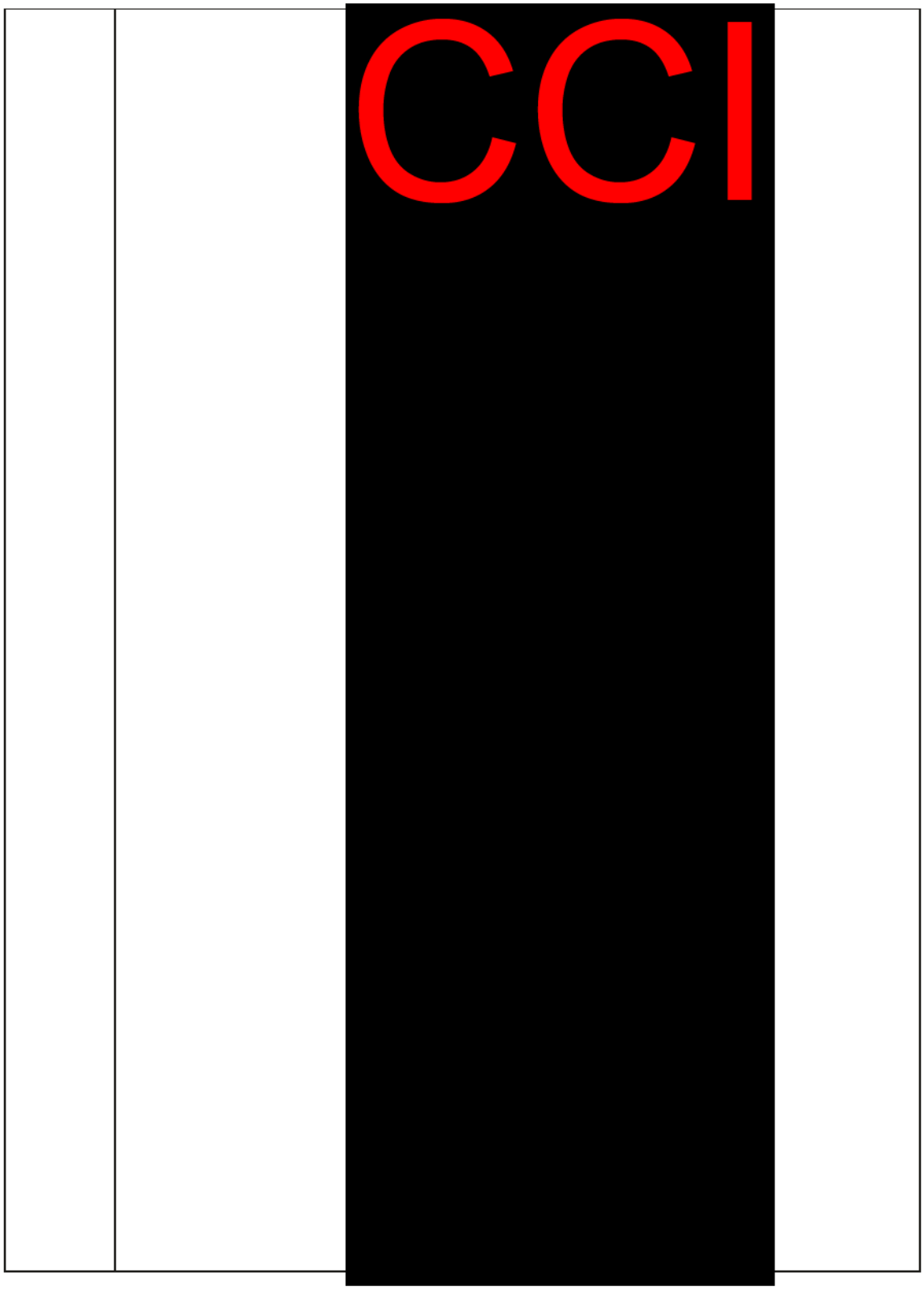
V2.0	20 DECEMBER 2022	[redacted]	Not Applicable
V2.1	24 MARCH 2023		Updates to v2.0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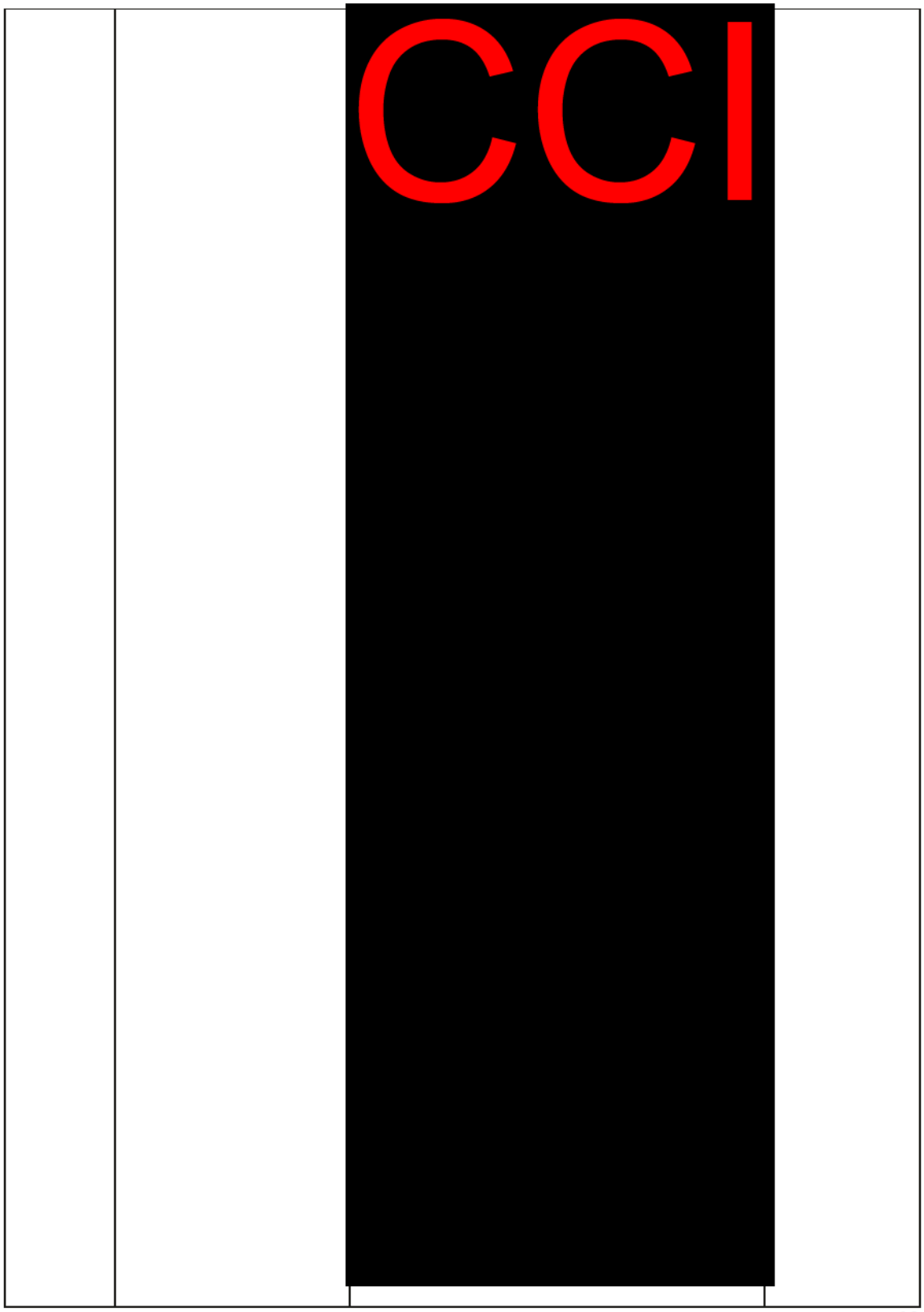
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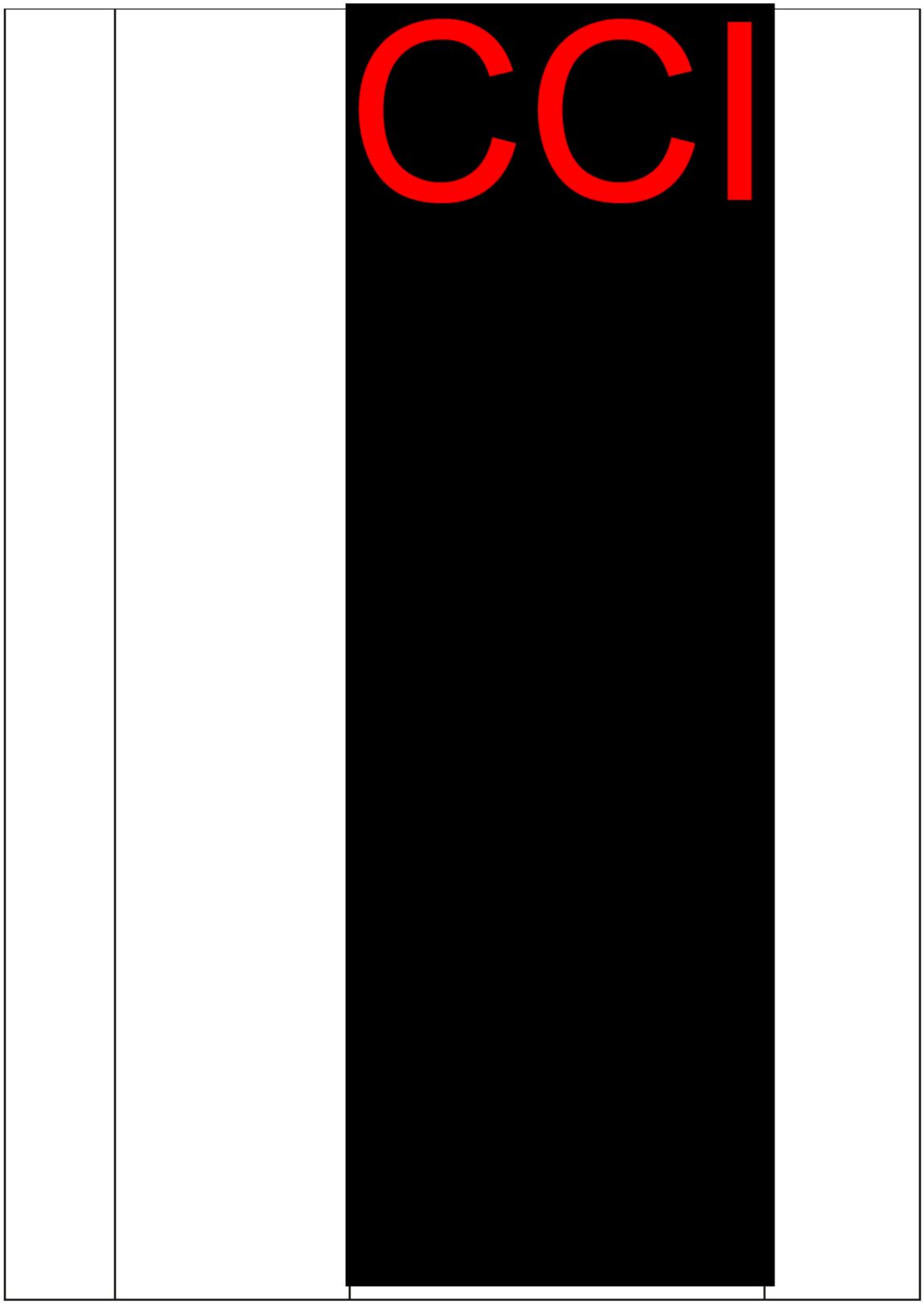
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V2.2	04 APRIL 2023		Updates to v2.1

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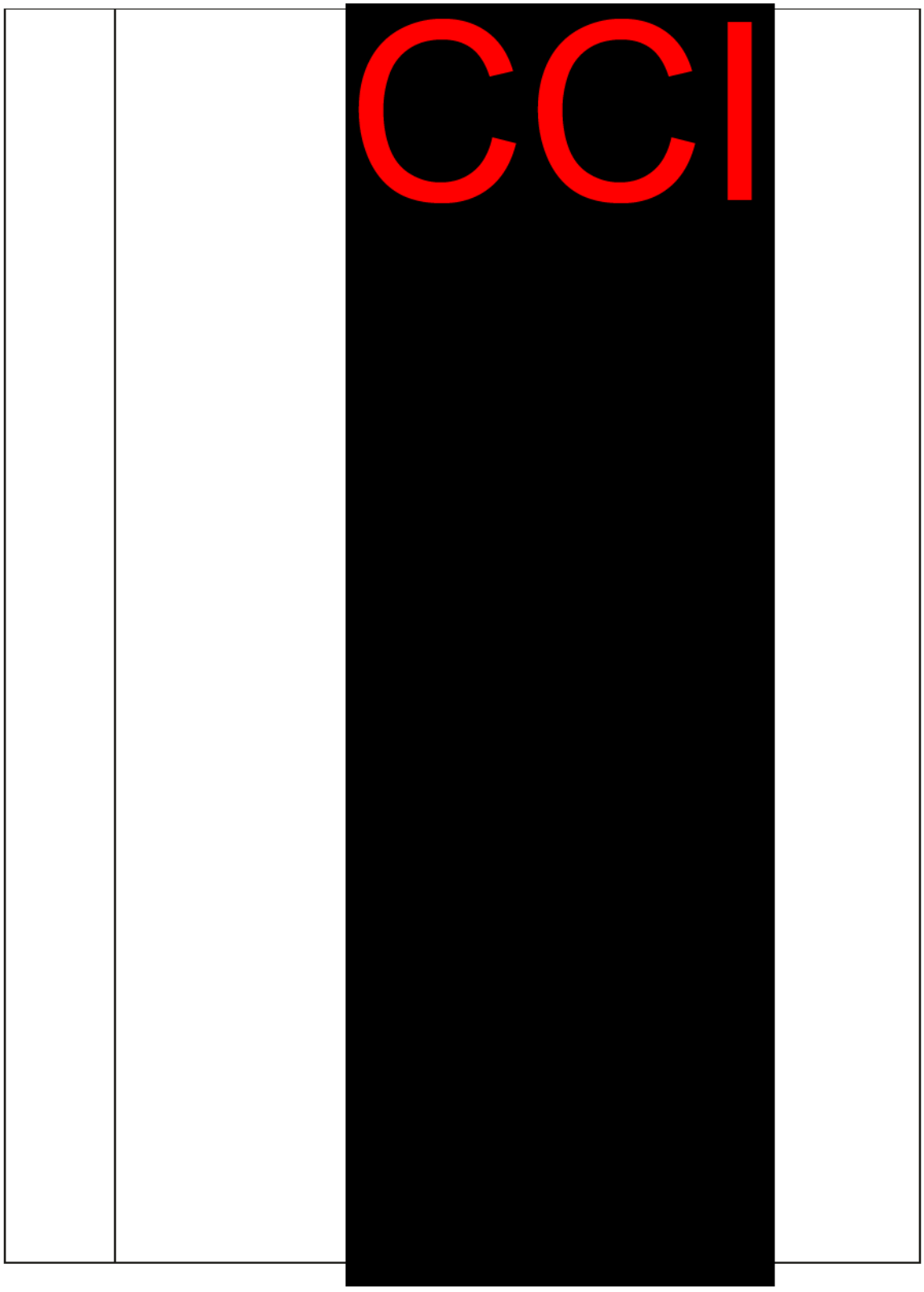
V3.0	04 APRIL 2023		
V3.1	11 JULY 2023		Updates to v3.0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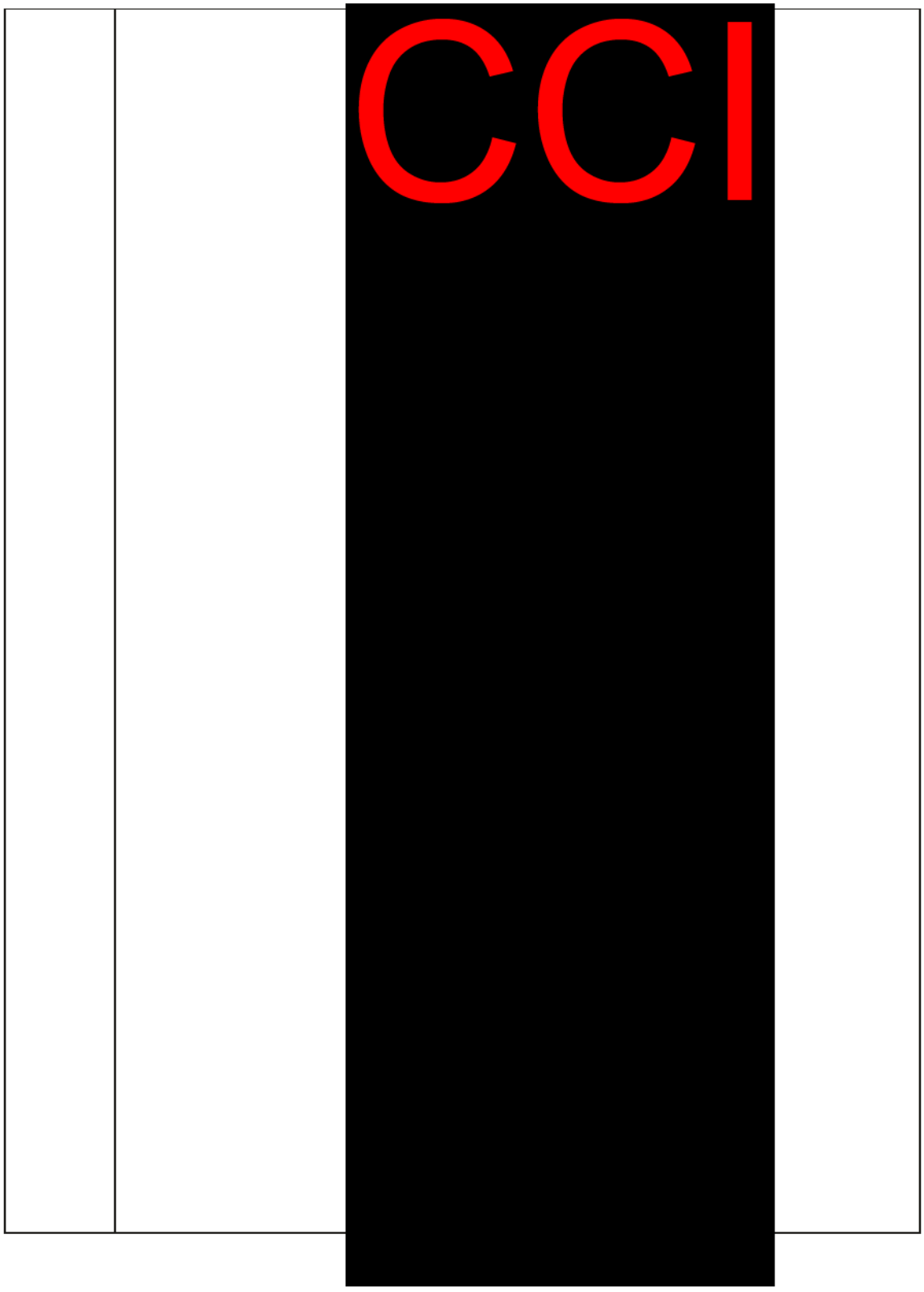
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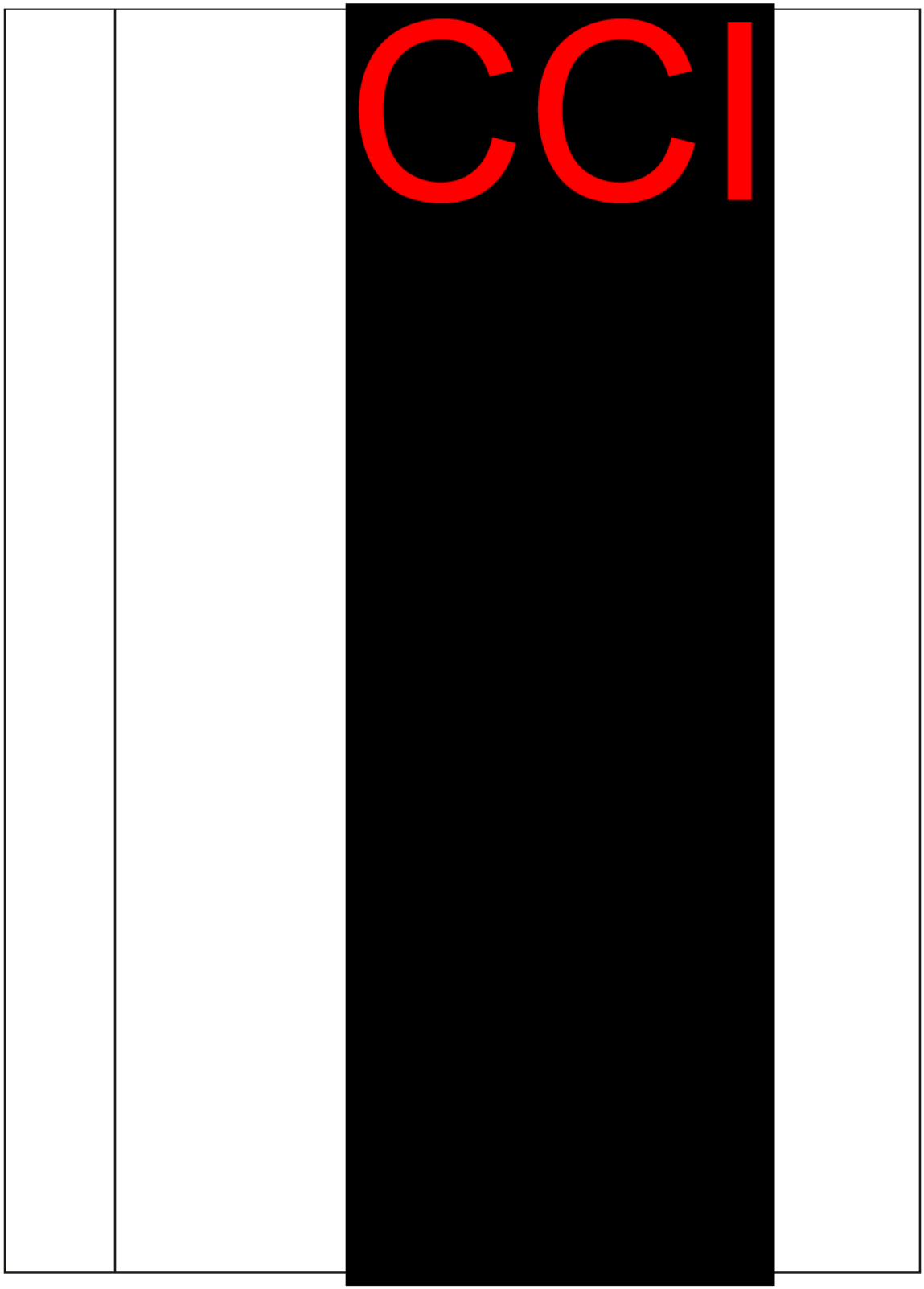
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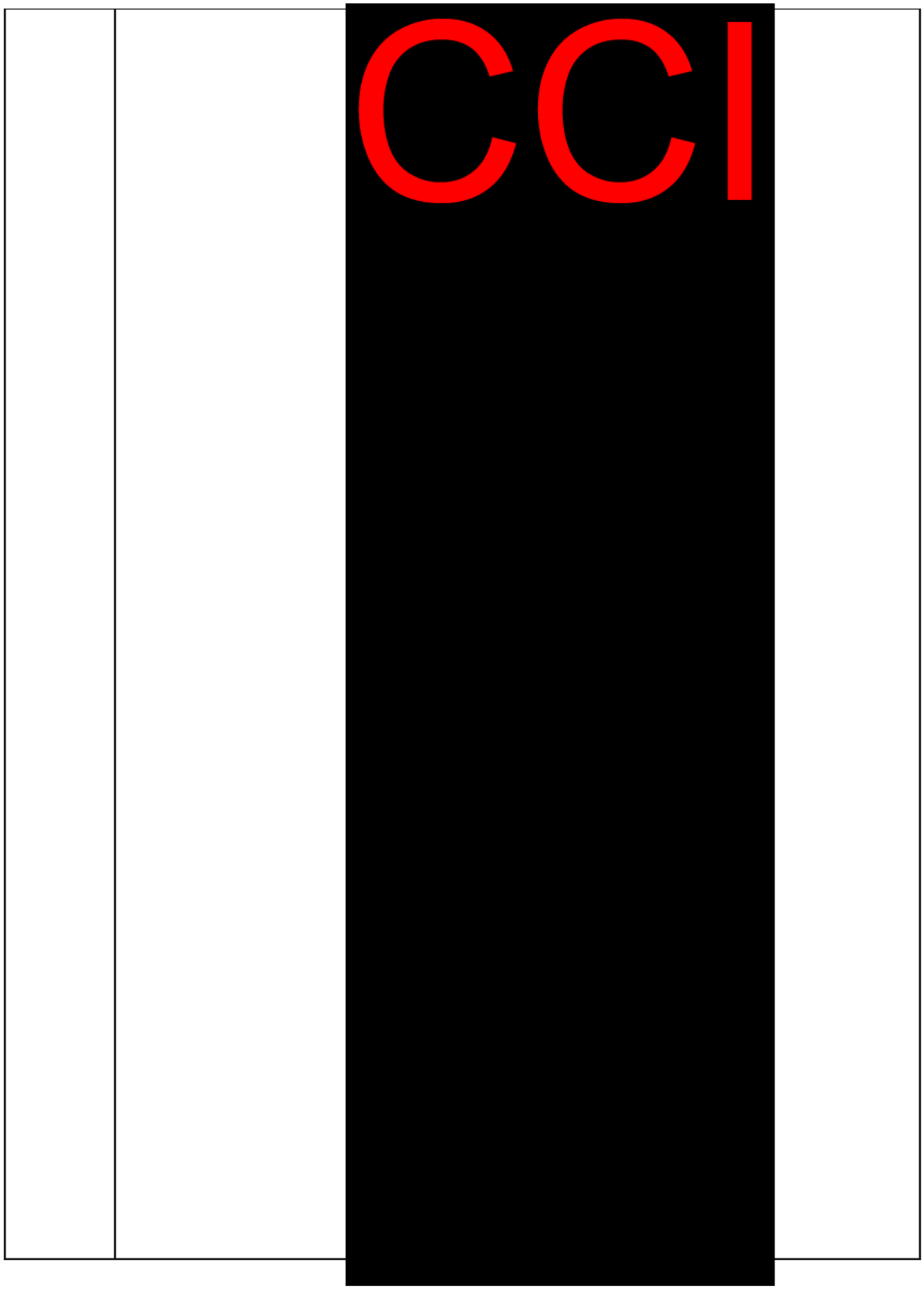
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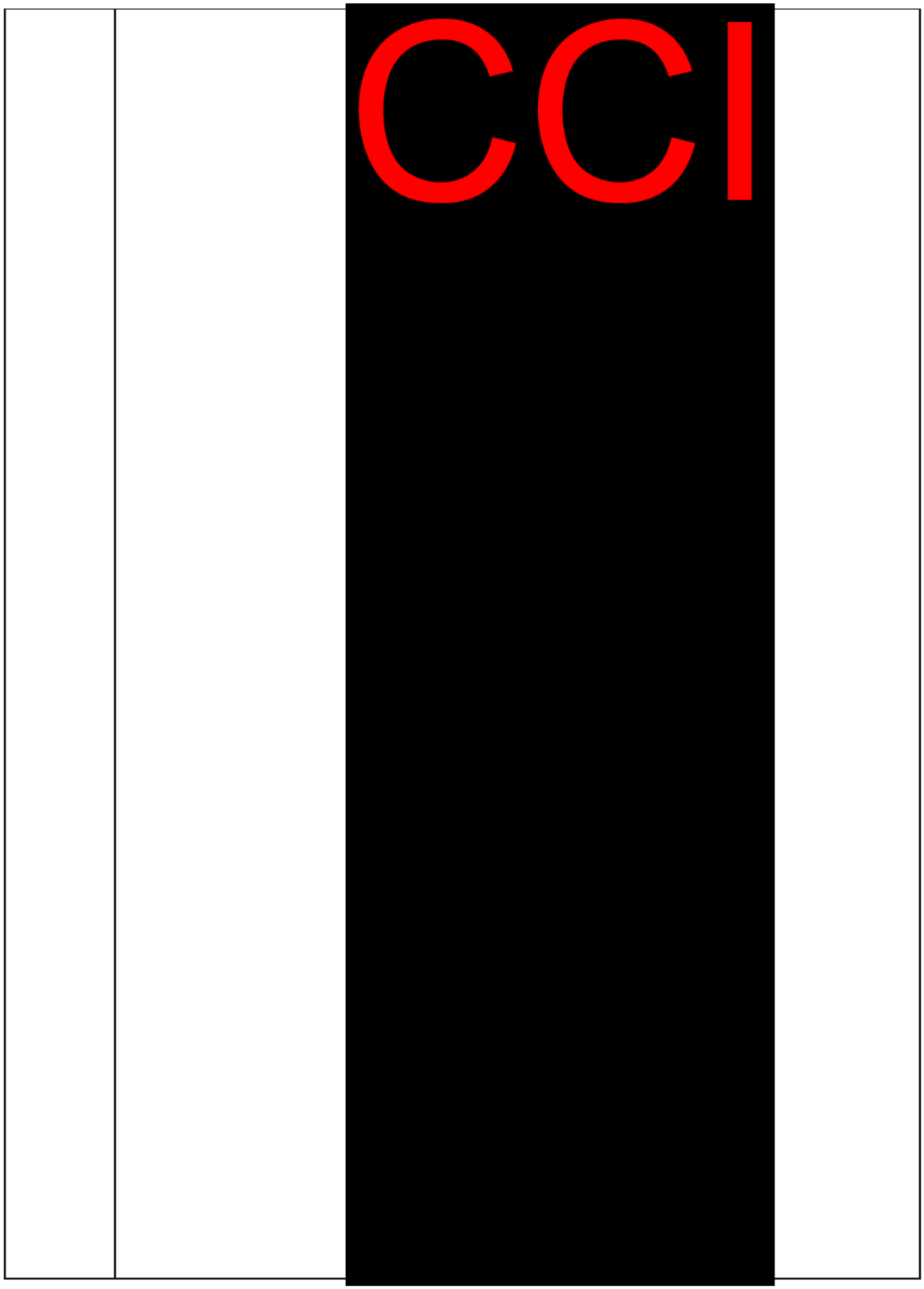
V3.2	21 JULY 2023		Updates to v3.1

		CCI	
V3.3	25 JULY 2023		Not applicable
V4.0	25 JULY 2023		Not applicable
V4.1	04 JUNE 2024		Updates to v4.0 as per Sponsor's requests to integrate SAP Addendum v1.0, and following protocol

		CCI	amendement 13 (version 14.0) dated 23 Feb 2024.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V4.2	12 JUNE 2024		Updates following resolution of pending points from SAP v4.1, and integration of Sponsor's requests.

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V4.3	20 JUNE 2024		Updates to SAP V4.2 following Sponsor's latest requests; All pending comments from SAP v4.2 solved.
V5.0	20 JUNE 2024		N.A.
V5.1	08 NOVEMBER 2024		Updates to SAP V5.0 following Sponsor's latest requests
V5.2	14 NOVEMBER 2024		Updates to SAP V5.1 based on Sponsor's review of v5.1; All pending comments from

		CCI	SAP v5.1 solved.
V6.0	14 NOVEMBER 2024		N.A.
V6.1	07 FEBRUARY 2025		Updates to SAP V6.0 following Sponsor's latest requests
V6.2	18 FEBRUARY 2025		Updates to SAP V6.1 based on Sponsor's review of v6.1
V7.0	19 FEBRUARY 2025		N.A.

2 List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
AML	Acute Myelogenous Leukemia
aPTT	Activated Partial Thromboplastin Time
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the concentration-time Curve
BID	Twice daily
BUN	Blood Urea Nitrogen
B2M	β2 microglobulin
CBC	Complete blood count
CI	Clinical Improvement
CHR	Complete Hematological Response
C_{max}	Concentration maximum
CR	Complete Response/Remission
CRO	Contract Research Organization
CRP	C-reactive Protein
CT	Computerised Tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Concentration trough
CSR	Clinical Study Report
DIC	Disseminated Intravascular Coagulation
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
ELN	European LeukemiaNet
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
EPO	Erythropoietin
ET	Essential Thrombocythemia
FDA	Food and Drugs Administration
GCP	Good Clinical Practice
HDL	High Density Lipoprotein
HU	Hydroxyurea
Hgb	Hemoglobin
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IL-8	Interleukin 8
INR	International Normalized Ratio
ITT	Intention-to-Treat
IWG	International Working Group
JAKI	JAK Inhibitor
K-M	Kaplan-Meier
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein

LOCF	Last Observation Carried Forward
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis
MFSAF	Myelofibrosis Symptom Assessment Form
mg	Milligram
mL	Millilitre
MPN	Myeloproliferative Neoplasms
MPN-SAF	Myeloproliferative Neoplasms Symptom Assessment Form
mRNA	Messenger Ribonucleic Acid
MRI	Magnetic Resonance Imaging
MRT	Myeloproliferative Neoplasms Research and Treatment
NCI	National Cancer Institute
ng	Nanogram
OHR	Overall Hematological Response
PD	Progressive Disease
PDAS	Pharmacodynamic Analysis Set
PE	Physical Examination
PGIC	Patient Global Impression of Change
PK	Pharmacokinetics
PKAS	Pharmacokinetics Analysis Set
PO	Per Oral; orally
PPIB	Peptidylprolyl Isomerase B
PPS	Per-Protocol Analysis Set
PR	Partial Response/Remission
PRO	Patient Reported Outcome
PT	Preferred Term
RBC	Red Blood Cell
RNA	Ribonucleic Acid
SAP	Statistical Analysis Plan
SAE	Serious adverse event
SAF	Safety Set
SD	Stable Disease
StD	Standard Deviation
SoC	System Organ Class
SOP	Standard Operating Procedure
TD	Transfusion Dependent
TE	Thromboembolic
TEAE	Treatment Emergent Adverse Event
TI	Transfusion Independent
T_{max}	Time to Maximum Concentration
TSS	Total Symptom Score
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organisation
β-hCG	beta-human chorionic gonadotropin

3 Introduction

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting of data collected for the Phase 2 - Myeloproliferative Neoplasms (MPN) expansion - portion of study CPI 0610-02 (MANIFEST). Pharmacokinetic (PK), pharmacodynamics, and predictive biomarker analyses will be described in separate documents.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials. All work planned and reported from this SAP will follow internationally accepted guidelines, published by the American Statistical Association and the Royal Statistical Society, for statistical practice.
Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided.
The planned analyses identified in this SAP will be included in clinical study reports (CSR) and/or in relevant summary report documents (e.g., regulatory submissions, abstract submissions or future manuscripts). Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data and will not require updating the final SAP. Any post-hoc, or unplanned, exploratory analysis performed will be clearly identified as such and described in the final Clinical Study Report (CSR).

The following documents were reviewed in preparation of this SAP:

- Clinical Trial Protocol CPI 0610-02 (MANIFEST). Version 14.0, dated 23 February 2024
- Electronic Case Report Rorm (eCRF) Version 20.0, dated 24-Apr-2024
- ICH Guidance on Statistical Principles for Clinical Trials (E9)

The reader of this SAP is encouraged to also read the aforementioned documents, for details on the design and planned conduct of this study. Any amendments to the protocol, which do not affect the statistical analyses, will not necessitate an update to this document.

4 Study Objectives and Endpoints

The table below reports the objectives and endpoints of the Phase 2 MPN-expansion study across arms, with indication on the primary, secondary, and exploratory nature of the endpoint, depending on arm and, where relevant, on cohort. The table is based on Tables 4, 5 and 6 of the clinical trial protocol.

Objective(s)	Endpoints	Arm (Cohort)	Type of endpoint
To evaluate the rate of conversion from Transfusion Dependent (TD) to Transfusion Independent (TI) in patients who enroll as TD.	Conversion rate is defined as the proportion of patients who convert from TD to TI.	1(A)	Primary
		2(A)	Primary
CCI		CCI	
To evaluate the duration of TI in patients who enrolled as TD.	The duration of TI is defined as the longest duration of RBC TI for patients who achieved TI $\geq$ 12 weeks during the treatment period.	1(A)	Secondary
		2(A)	Secondary
CCI		CCI	
To evaluate the change in patient-reported outcomes (PROs) and the rate of $\geq$ 50% reduction in Total Symptom Score (TSS) after 12 and 24 weeks of treatment.	PROs will be evaluated using the Myelofibrosis Symptom Assessment Form (MFSAF) v4.0 and the Patient Global Impression of Change (PGIC). Changes from baseline in the TSS from the MFSAF v4.0 and the PGIC will be described. The proportion of patients who achieve a $\geq$ 50% reduction in TSS after 12 weeks (Cycle 5, Day 1) and 24 weeks of treatment (Cycle 9, Day 1) will also be reported.	1(A)	Secondary
		1(B)	Secondary
		2(A)	Secondary
		2(B)	Secondary
		3	Secondary
CCI			

[redacted]

To evaluate splenic response rate by imaging after 24 weeks of treatment.	The splenic response rate is defined as the proportion of patients who achieve a ≥ 35% reduction from baseline spleen size by imaging (MRI or CT) after 24 weeks of treatment (Cycle 9, Day 1).	1(A)	Secondary
		1(B)	Primary
		2(A)	Secondary
		2(B)	Primary
		3	Primary
To evaluate splenic response rate by imaging after 12 weeks of treatment.	The splenic response rate is defined as the proportion of patients who achieve a ≥ 35% reduction from baseline spleen size by imaging (MRI or CT) after 12 weeks of treatment (Cycle 5, Day 1).	1(A)	Secondary
		1(B)	Secondary
		2(A)	Secondary
		2(B)	Secondary
		3	Secondary
To evaluate the overall splenic response (SVR35) rate.	The overall splenic response rate is the proportion of patients who achieve a ≥ 35% reduction from baseline spleen size by imaging (MRI or CT).	1(A)	Secondary
		1(B)	Secondary
		2(A)	Secondary
		2(B)	Secondary
		3	Secondary

[redacted]

To evaluate the duration of splenic response (SVR35).	Duration of the spleen response is defined as the time when splenic response criteria are first met (i.e., a ≥ 35% reduction from baseline spleen size) until the time at which spleen volume reduction is < 35% and is increased by ≥ 25% from the nadir in spleen volume by imaging.	1(A)	Secondary
		1(B)	Secondary
		2(A)	Secondary
		2(B)	Secondary
		3	Secondary

[redacted]

[redacted]

To evaluate the early anemic response rate in patients who enroll as TD.	The early anemic response rate is defined as the proportion of patients who achieve a Hgb increase ≥ 1 g/dL from baseline over any consecutive 8-week period in the absence of RBC transfusions.	1(A)	Secondary
		2(A)	Secondary

[redacted]

To evaluate the anemic response rate in patients who are non-TD at enrolment.	The anemic response rate is defined as the proportion of patients who are non-TD at enrolment and achieve ≥ 1.5 g/dL Hgb increase from baseline over any consecutive 12-week period in the absence of RBC transfusions.	1(B)	Secondary
		2(B)	Secondary
		3	Secondary

[redacted]

CPI-0610 in patients with MF and ET.	changes from baseline in vital signs, and laboratory values.		
		1(B)	Secondary
		2(A)	Secondary
		2(B)	Secondary
		3	Secondary

		4	Secondary
To characterize the PK of CPI-0610.	C_{max}, t_{max}, C_{trough}, AUC_{last}, $AUC_{0-8,ss}$, $C_{max,ss}$, $t_{max,ss}$	1(A)	Secondary
		1(B)	Secondary
		2(A)	Secondary
		2(B)	Secondary
		3	Secondary
		4	Secondary
To characterize the effects, if any, of CPI-0610 on the PK of ruxolitinib.	C_{max}, t_{max}, C_{trough}, AUC_{last}, $AUC_{0-8,ss}$	2(A)	Secondary
		2(B)	Secondary
		3	Secondary

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To evaluate the complete hematological response (CHR) rate.	The rate is defined as the proportion of patients who meet the criteria for a CHR, as assessed by modified European LeukemiaNet (ELN) criteria: - Normalization of platelet count (≤ 400 x 10^9/L) - White blood cell (WBC) count within normal range (≤ 10 x 10^9/L) - Laboratory results confirmed after 1 cycle (after 3 weeks) - Normal spleen size (by palpation or imaging).	4	Primary
To assess symptom improvement.	The proportion of patients with ≥ 50% reduction from baseline in the MPN-SAF total score. PGIC will also be summarized.	4	Secondary

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To evaluate the partial hematological response rate.	The rate is defined as the proportion of patients who meet the following	4	Secondary

	criteria for a partial hematological response: - Platelets 400-600 x 10^9/L - WBC within normal range (≤ 10 x 10^9/L) - Laboratory results confirmed after 1 cycle (after 3 weeks).		
To evaluate the overall hematological response rate and duration of response.	The rate is defined as the proportion of patients with either a complete or partial hematological response at any time point, and duration of response.	4	Secondary
To evaluate the composite rate of overall hematological response and symptom improvement.	This composite rate is defined as the proportion of patients who achieve both an overall hematological response and ≥ 50% reduction in TSS from the MPN-SAF throughout the study.	4	Secondary
To evaluate the duration of the composite overall hematological response and symptom improvement from the MPN-SAF.	The duration of this composite response is defined as the time from the first onset date to loss of response, including: - Overall hematologic response - Symptom improvement as measured from the MPN-SAF.	4	Secondary
To evaluate the rate of hemorrhagic and thromboembolic events.	The rate is defined as the proportion of patients with hemorrhagic or TE events.	4	Secondary

[redacted]


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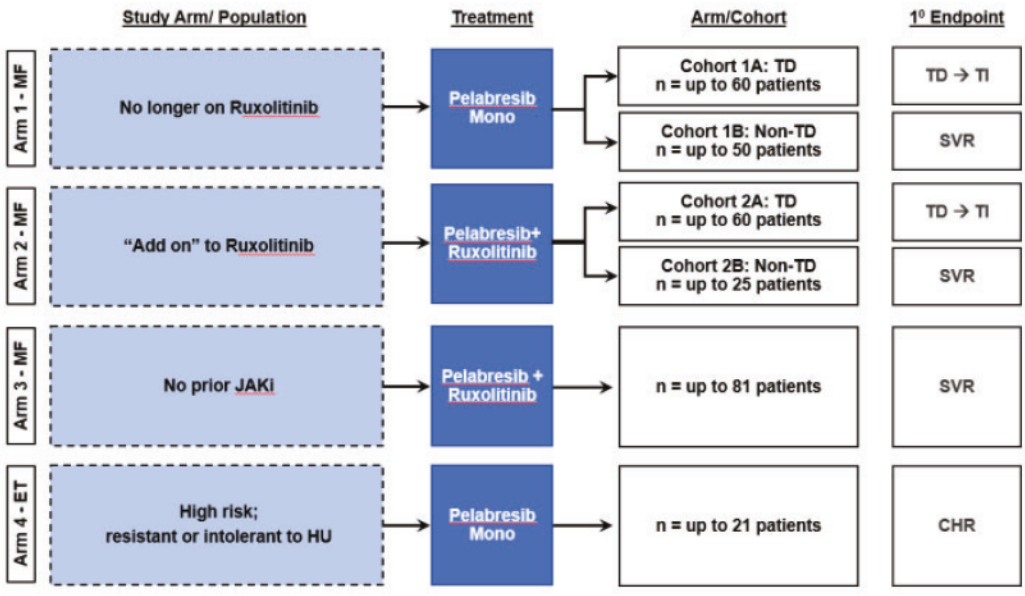
5 Study design

5.1 General overview

This is a Phase 1/2, multi-center, open-label, dose escalation study (Phase 1) of CPI-0610 in patients with acute leukemia, myelodysplastic syndrome, myeloproliferative neoplasm or myelofibrosis and an expansion study (Phase 2) of CPI-0610 in patients with Myelofibrosis (MF) (arms 1, 2, and 3) and in high-risk patients with Essential Thrombocythemia (ET) (arm 4). More in detail, the Phase 2 expansion study evaluates CPI-0610 in: patients with MF previously or currently treated with a JAKi as a single agent (arm 1) and in combination with ruxolitinib (arm 2); patients with MF who are JAKi naïve in combination with ruxolitinib (arm 3); and in high-risk patients with ET who are resistant or intolerant to hydroxyurea (HU) (i.e., arm 4; see below). Arms 1 and 2 are further stratified into TD cohorts (cohorts 1A and 2A) and non-TD cohorts (cohorts 1B and 2B) - see Figure 1 below for a schematic illustration of the study design.

During Phase 2, up to 60 evaluable MF patients are enrolled in each of Cohorts 1A and 2A, up to 50 evaluable MF patients in Cohort 1B, and up to 25 evaluable MF patients in Cohort 2B - Arms 1 and 2. Up to 81 evaluable patients are enrolled in Arm 3, and up to 21 evaluable ET patients are enrolled in Arm 4 - Figure 1. Therefore, approximately 297 patients are enrolled into the Phase 2 study. Additional patients may also be enrolled if replacement of non-evaluable patients is needed.

Figure 1: Study Design Schematic



CHR = complete hematological response; ET = Essential thrombocythemia; HU = hydroxyurea; MF = myelofibrosis; SVR = spleen volume response; TD = transfusion dependent; TI = transfusion independent.

The primary objective of Phase 2 expansion study depends on arm and cohort. The primary objective in Cohorts 1B and 2B and in arm 3 is to evaluate splenic response rate by imaging after 24 weeks of treatment. The primary objective in Cohorts 1A and 2A is to evaluate the rate of conversion from

transfusion dependence to transfusion independence. The primary objective in arm 4 (ET) is to evaluate the complete hematologic response rate.

In both phases of the study, CPI-0610 (pelabresib) is administered orally, once a day for 14 consecutive days followed by a 7-day break, with cycles of treatment repeated every 21 days (1 cycle = 21 days; i.e., 14 days of CPI-0610 + 7-day break). Patients in Arms 2 (Add-on to JAKi Combination arm) and 3 (JAKi Naïve Combination arm) also receive ruxolitinib orally twice a day on a continuous basis for 21 consecutive days of each 21-day cycle. Cycles of treatment are repeated as long as the patient's disease has not progressed or until precluded by toxicity.

Patients are seen in the clinic by the investigator during Screening and on Day 1 and Day 14 of Cycle 1. Subsequently, patients are seen in the clinic by the investigator and study personnel on Day 1 of each new cycle of treatment to assess their well-being and compliance with the study. An End of Treatment (EOT) visit is required for all patients within 7 days of the last dose of study treatment. An End of Study (EOS) visit is required within 30 days from the last dose of CPI-0610.

Final analysis will take place when all patients have finished their EOS visit.

5.2 Planned Analyses

5.2.1 Primary analysis

A primary analysis is planned and its results will be reported in the primary CSR.

The primary analysis will take place when all patients have either completed their primary endpoint assessment (i.e., week 24 visit) or discontinued prematurely (see Protocol v14.0, section 8.1.1).

5.2.1.1 Analyses to be performed

The primary analysis will be conducted on Arm 1 (both cohorts), Arm 2 (both cohorts) and Arm 3. For Arms 1, 2 and 3, all analyses specified in this SAP will be performed for the primary analysis. These include primary and secondary efficacy endpoints analyses as well as safety analyses, patient disposition, and baseline and demographic characteristics.

5.2.1.2 Data cutoff and data cleaning

For the purpose of the primary analysis, a data cutoff is planned when all patients have either completed their primary endpoint assessment of discontinued prematurely.

All data required for the analyses specified in this SAP will be cleaned, reconciled, and source data verified as applicable.

Any data collected beyond the data cutoff date will not be included in the primary analysis. Only data with an assessment date or event start date (e.g., vital sign assessment date or start date of an adverse event [AE]) prior to or on the cutoff date will be included in the analysis. For example, if the cutoff date is 15 June 2020, then an AE starting on 13 June 2020 will be reported, whereas an AE with start date on 17 June 2020 will not be reported.

All events with an event start date either before or on the cutoff date and an event end date after the cutoff date will be reported in listings as "ongoing" (the end date is missing in listings). The same rule applies to events starting either before or on the cutoff date and not having documented end date.

If it is required to impute an end date, the missing end date is replaced by the cutoff date and is flagged in the listings.

5.2.1.3 Extent of unblinding

This is an open-label study and (un)blinding is not applicable.

5.2.2 Final analysis

The final analysis will be performed at study end. Data will be reported in the final CSR. The study end and final analysis are expected to occur when all patients have finished their EOS visit (see Protocol v14.0, section 8.1.1). All endpoints will be analyzed for the final analysis.

For final analysis, the cutoff date will be replaced by the EOS date (the date of the EOS visit for each subject). Refer to section 21.2 for details on handling cases of missing EOS date or EOS date < date of last contact.

5.2.2.1 Analyses to be performed

The final analysis will be conducted on Arm 1 (both cohorts), Arm 2 (both cohorts), Arm 3 and Arm 4. All analyses specified in this SAP will be conducted.

5.2.2.2 Data cleaning

Data will be cleaned, reconciled, and source data verified as applicable.

5.2.2.3 Extent of unblinding

This is an open-label study and (un)blinding is not applicable.

5.3 Sample size determination

Since this study is not a randomized control confirmatory trial, the purpose of sample size calculation is exploratory. The final sample size might be different than the original planned. See clinical trial protocol v14.0 (27-FEB-2024), section 8.1.1.

5.4 Randomization and stratification factors

No randomization is used in this trial. In the prior (i.e., Arm 1) and Add-on (i.e., Arm 2) JAKi arms, based on TD status at enrolment, patients are stratified into TD cohorts (Cohorts 1A and 2A) and non-TD cohorts (Cohorts 1B and 2B) - see section 6.1.1 for details about treatment arms and cohorts.

6 Definitions

6.1 General definitions

6.1.1 Treatment Arms

The Phase 2 expansion study evaluates CPI-0610 in the 4 arms as described below.

Arm 1: Prior JAKi Monotherapy Arm (MF patients treated with CPI-0610 alone)

Arm 1 consists of the following 2 cohorts:

- Cohort 1A: Patients with MF who are TD (defined as receiving ≥ 6 units of RBC transfusions over the 12 weeks prior to enrolment) and who have previously been treated with a JAKi and are intolerant, resistant, refractory or lost response to the JAKi, or are ineligible to be treated with a JAKi.
- Cohort 1B: Patients with MF who are not TD and who have previously been treated with a JAKi and are intolerant, resistant, refractory or lost response to the JAKi, or are ineligible to be treated with a JAKi.

Arm 2: Add-on to JAKi Combination Arm (MF patients treated with CPI-0610 in combination with ruxolitinib)

Arm 2 consists of the 2 following cohorts:

- Cohort 2A: Patients with MF who are TD and are currently taking ruxolitinib for > 6 months and be on a stable dose for a minimum of 8 weeks prior to the start of the study drug but have disease that is not being adequately controlled by ruxolitinib.
- Cohort 2B: Patients with MF who are not TD and are currently taking ruxolitinib for > 6 months and be on a stable dose for a minimum of 8 weeks prior to the start of the study drug but have disease that is not being adequately controlled by ruxolitinib.

Arm 3: JAKi Naïve Combination Arm (MF patients treated with CPI-0610 in combination with ruxolitinib):

- Patients with MF who are eligible for ruxolitinib and have not previously received a JAKi. Patients included in Arm 3 are treated with CPI-0610 in combination with ruxolitinib.

Arm 4: ET Arm (high-risk ET patients treated with CPI-0610 alone):

- High-risk ET patients who are resistant or intolerant to HU.

Patients are assigned to a treatment arm based on the TAMFGRP value entered for question 8 (*Myelofibrosis Arm*) in the 'Treatment Assignment (TA) eCRF page:

- If TAMFGR = 1, the patient is assigned to Arm 1 - i.e., Monotherapy Arm (MF patients treated with CPI-0610 alone);

- If TAMFGR = 2, the patient is assigned to Arm 2 - i.e., Combination Arm (MF patients treated with CPI-0610 in combination with ruxolitinib);

- If TAMFGR = 3, the patient is assigned to Arm 3 - i.e., JAKi Naïve Combination Arm (no prior JAKi treatments in combination with ruxolitinib);

- If TAMFGR = 4, the patient is assigned to Arm 4 - i.e., ET arm (high-risk ET patients treated with CPI-0610 alone).

In addition, for Arms 1 and 2, patients will be assigned to TD (i.e., cohorts 1A and 2A) or non-TD cohorts (i.e., cohorts 1B and 2B) based on what follows:

- If the answer to question 1 (i.e., 'Is the subject transfusion dependent?') in the 'Transfusions History (TH) eCRF page is "Yes", then the patient will be assigned to TD cohorts (i.e., cohorts 1A or 2A, depending on arm assignment);

- If the answer to question 1 (i.e., 'Is the subject transfusion dependent?') in the 'Transfusions History (TH)' eCRF page is "No", then the patient will be assigned to non-TD cohorts (i.e., cohorts 1B or 2B, depending on arm assignment).

6.1.2 Study Drug

In this study, study drug refers to CPI-0610 (pelabresib).

6.1.3 Study Treatment

Study treatment refers to:

Arm 1: CPI-0610 alone

Arm 2: CPI-0610 in combination with ruxolitinib.

Arm 3: CPI-0610 in combination with ruxolitinib.

Arm 4: CPI-0610 alone

Study treatment completion is defined, for all arms, as the date of last administration of CPI-0610 (see section 6.1.5.2).

The rules for study treatment completion apply also to study drug completion.

6.1.4 Treatment cycle

A complete treatment cycle is defined as 21 calendar days during which CPI-0610 is administered for 14 consecutive days followed by a 7-day break (1 cycle = 21 days; i.e., 14 days of CPI-0610 + 7-day break). In Arms 2 and 3, for each cycle, ruxolitinib is administered on a continuous basis for the 21 consecutive days of each cycle.

Details on by-cycle assessments are provided in section 23.

6.1.5 Dates of study drug administration/study treatment administration

6.1.5.1 Date of first administration of study drug

The date of first administration of study drug is the date of first dose received for the study drug, as collected in eCRF page "CPI-0610 Administration C1 (14-days Daily Dosing) (DA_1)".

6.1.5.2 Date of last administration of study drug

The date of last administration of study drug is the date of last dose received for the study drug.

6.1.5.3 Date of first administration of study treatment

The date of first administration of study treatment is the date of first administration of any study treatment component.

6.1.5.4 Date of last administration of study treatment

The date of last administration of study treatment is the latest date of non-zero dose administration of any study treatment component. For example, for arms 2 and 3, the date of last administration of ruxolitinib ideally will be the date of last administration of study treatment. The safety information up to 30 days after the last dose of CPI-0610 was taken will be collected and then the long-term follow-up for the study drugs will be started.

6.1.6 Reference start date and study day: C1D1

C1D1 is defined as the date of Cycle 1 Day 1 visit. This is also considered as Study Day 1.

The day prior to C1D1 is considered as Day -1.

6.1.7 End of Treatment date

EOT date is defined as the date of the EOT visit. See section 23 for details on EOT visit; see section 21.2 for details on handling of missing data.

6.1.8 End of Study date

End of Study (EOS) date is defined as the date of the EOS visit. See section 23 for details on EOS visit; see section 21.2 for details on handling of missing data.

6.1.9 Date of Last Contact

The last contact date is derived for patients not known to have died at the analysis cutoff date and for censoring of patients, based on the latest complete date among the following:

- Actual assessment dates – Scheduled or unscheduled visits (labs, vital signs, performance status, tumor imaging, end of treatment (EOT) completion, end of study, screening failure, etc.),
- Anti-cancer therapies administered after study drug discontinuation,
- Date of any procedure (e.g., surgery / radiation therapy date),
- AE start or end dates,
- Study treatment start/end date,
- "Date of last patient contact" as reported on the "Subject Disposition - End of Treatment (DS)" eCRF page,
- End of Study Visit Date from "Subject Disposition - End of Study" eCRF page,
- Date of Last Known to be Alive from the "30-day Safety Follow-up", "Long Term Follow-up" or "Survival Follow-up" eCRF pages.

For subjects who died, if the date of last contact > date of last known to be alive, then the date of last known to be alive will be considered as the date of last contact. The last contact date is defined as the latest complete date from the above list or the cutoff date whichever comes first, i.e., imputed dates are not valid.

The last contact date is used for censoring of patients in the analysis of time-to-event endpoints (see censoring strategy and rule in section 8.5.3.2).

6.1.10 Definition of prior therapies, prior and concomitant medications

Prior therapies:

Prior therapies will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior therapies are recorded in the "Prior Therapy (MPT)" eCRF page and are defined as any therapy with an end date prior to the date of first administration of study treatment (section 6.1.5.3)

Prior medication:

Prior medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). These are recorded in the "Prior/Concomitant Medications (CM)" eCRF page, and are defined as any medication with an end date prior to the date of first administration of study treatment (section 6.1.5.3). See section 21.4 for handling of missing/partial dates.

Concomitant medication/non-drug therapies:

Concomitant therapies will be coded using the World Health Organization Drug Dictionary (WHO-DD). These are collected at screening as well as throughout the study and up to 30 days after the last dose of study drug (see section 23 for details on schedule of events and section 6.1.5.2 for date of last dose of study drug). Concomitant medications are recorded on the "Prior/Concomitant Medications (CM)" eCRF page and are defined as follows:

- Any medication that is initiated before the date of first intake of study treatment and terminated after this date (section 6.1.5.3), or initiated on or after the date of first administration of study treatment up to the date of last administration of study treatment (section 6.1.5.4 or ongoing at end of study (i.e., the checkbox for question 2.R.8 "Ongoing?" is ticked "Yes" in the corresponding eCRF page), in the ITT analysis set.

See section 21.4 for handling of missing or partial dates for concomitant medications.

6.1.11 Screening failure

Patients who signed the informed consent form, but failed to fulfil the inclusion/exclusion criteria, are considered as screening failures. Reasons for screening failures will be presented in the listings of patient disposition and inclusion/exclusion criteria. The reasons for screening failure will also be summarized.

6.1.12 Baseline

Baseline is the result of an investigation describing the "true" uninfluenced state of the patient. Unless otherwise specified in the next sections, baseline is defined as the period from the date of signing any informed consent document to the start date of study treatment (i.e., C1D1, section 6.1.6). Assessments specified to be collected post-dose on the first date of treatment (e.g., vital signs assessments) are not considered as baseline values.

Change from baseline calculation

Absolute change from baseline will be calculated as

[visit value – baseline value]

and percentage change from baseline will be calculated as

$$\left[\frac{\text{visit value} - \text{baseline value}}{\text{baseline value}} \times 100\right].$$

6.1.13 Baseline for Spleen Volume Endpoints

For all spleen volume-related endpoints, baseline spleen volume is the latest non-missing MRI or CT assessment for spleen volume value on or before C1D1 (see section 6.1.6 for C1D1 definition).

6.1.14 Baseline for TSS

Baseline for the Total Symptom Score (TSS) as measured by the MFSAF v4.0 or by the MPN-SAF is defined as the average of non-missing daily total symptom scores over the 7-day period on or prior to C1D1 (section 6.1.6) and after ICF signature date. If the average of non-missing daily total symptom scores over the 7-day period on or prior to C1D1 is missing, the most recent non-missing weekly average TSS assessment on or prior to C1D1 will be considered as baseline.

6.1.15 Baseline for Early Anemic Response Rate and Anemic Response Rate

After applying the 14/3-day rule, the baseline Hgb value is defined as the latest Hgb value from the local laboratory, collected on or prior to the first dose of CPI-0610. Any transfusion record collected within 42 days on or prior to the first dose of CPI-0610 will be valid for the analysis. If, after applying the 14/3-day rule, no valid assessments are available, then baseline for early anemic response and for anemic response will be considered as missing.

6.1.16 Baseline for Bone Marrow Fibrosis Grade

Baseline for bone marrow fibrosis grade is defined as the most recent non-missing bone marrow fibrosis grade record collected prior to C1D1 (section 6.1.6).

6.1.17 Baseline for Safety Evaluations

For safety evaluations (i.e., laboratory data, vital signs and ECG) baseline is defined as the last non-missing assessment, including unscheduled assessments, on or before the date of first administration of study drug (section 6.1.5.1) and on or after ICF signature date. For assessments where exact time of the assessment has been collected, the assessment time will be used to identify baseline evaluations that take place on the same day as the first study drug administration.

If patients have no value as defined above, the baseline result will be missing.

6.1.18 Adverse events

Any event recorded in the Adverse Events pages of the eCRF.

6.1.18.1 Treatment-emergent Adverse Event (TEAE)

TEAE is defined as any AE that occurs in the following time interval (including the lower and upper limits): [Date of administration of first dose of study treatment (section 6.1.5.3); Date of administration of last dose of study drug (i.e., CPI-0610; section 6.1.5.2) + 30 days], or before the start of alternative (off-study) treatment for MF (i.e., new anti-cancer therapy), whichever occurs first.

If the start date and time of an AE are partially or completely missing, the AE will be assumed to be a TEAE if it cannot be definitively shown that the AE did not occur or worsen during the treatment-emergent period (worst case approach).

The methods for handling missing dates for defining a TEAE is depicted in section 21.3.

6.1.18.2 Study Drug-related Adverse Event

A study drug-related AE is an event that is reported in the Adverse Events eCRF pages and marked with values 1-to-3 (i.e., respectively, 'Definitely related', 'Probably related', 'Possibly related' ") for question 'Is there a reasonable possibility that this AE/SAE may have been related to the study treatment?'.

6.1.18.3 Adverse Event Related to Ruxolitinib

An AE related to ruxolitinib is an event that is reported in the AEs eCRF pages and marked with values 1-to-3 for question 'Is there a reasonable possibility that this AE/SAE may have been related to the ruxolitinib dosing?'.

6.1.18.4 Serious Adverse Event (SAE)

A SAE is defined as any AE recorded as serious in the eCRF by the tick box 'Yes' for question 'Was the event serious?'.

6.1.18.5 Adverse Events leading to death

An AE leading to death is defined as any AE with outcome 'Fatal' and/or "Seriousness criteria: Results in death" marked as "Yes" in the eCRF).

6.1.18.6 Adverse Events requiring dose adjustment

For CPI-0610: an AE requiring dose adjustment is an event that is reported in the AE eCRF pages and marked with values 2 or 3 (i.e., "Dose increased" and "Dose reduced", respectively) for the field "Study Drug Action Taken".

For ruxolitinib: an AE requiring dose adjustment is an event that is reported in the AE eCRF pages and marked with values 2 or 3 (i.e., "Dose reduced" and "Dose increased", respectively) for the field "Action taken with Ruxolitinib dose").

6.1.18.7 Adverse Events requiring study drug interruption

An AE requiring study drug interruption is an event that is reported in the AE eCRF pages and marked with value 4 (i.e., "Drug interrupted") for the field "Study Drug Action Taken" with respect to CPI-0610.

6.1.18.8 Adverse Events requiring additional therapy

An AE requiring additional therapy is an event that is reported in the AE eCRF pages and marked with values 10 and/or 11 (i.e., "Required Concomitant Medication" and "Required Procedure", respectively) for the field "Action Taken to AE".

6.1.18.9 **Pre-Treatment Adverse Event**

Any AE started prior to the first administration of study treatment date/time (section 6.1.5.3) will be classified as Pre-treatment AE.

6.1.18.10 **AEs of Special Interest (AESIs)**

AEs of special interest (AESIs) are identified below.

1) Treatment discontinuation syndrome. This consists of the exacerbation of MF symptoms following interruption or discontinuation of study treatment. Treatment discontinuation syndrome includes any TEAEs with onset date within 30 days after the date of CPI-0610 discontinuation or before the start of alternative (off-study) treatment to MF (i.e., new anti-cancer therapy), whichever is earlier.
2) Acute respiratory distress syndrome (ARDS). This includes all AEs with the following PTs:

– Acute respiratory distress
– Acute respiratory distress syndrome
– Respiratory distress
– Respiratory failure
– Acute respiratory failure
– Severe acute respiratory failure.

3) Accelerated phase (≥ 10% and < 20% blasts): confirmed by bone marrow biopsy, or by 2 consecutive peripheral blood measurements. Events of accelerated phase are identified by the following PT:

    - Blast cell count increased.

4) Transformation to blast phase (≥ 20% blasts): confirmed by a bone marrow blast count of ≥ 20%, or peripheral blood blast count of ≥ 20% associated with absolute blast count of ≥ $1x10^9$/L that persists for at leats 2 weeks.

    Events of transformation to blast phase are identified by the following PTs:

    - Acute erythroid leukaemia
    - Acute leukaemia
    - Acute leukaemia in remission
    - Acute megakaryocytic leukaemia
    - Acute monocytic leukaemia
    - Acute monocytic leukaemia (in remission)
    - Acute myeloid leukaemia

- Acute myeloid leukaemia (in remission)
- Acute myeloid leukaemia recurrent
- Acute myeloid leukaemia refractory
- Acute myelomonocytic leukaemia
- Acute promyelocytic leukaemia
- Acute undifferentiated leukaemia
- Leukaemia
- Leukaemia granulocytic
- Myeloid leukaemia
- Leukaemia monocytic
- Chloroma
- Chloroma (in remission)
- Transformation to acute myeloid leukaemia

6.1.18.11 COVID-19 related AEs

COVID-19 related AEs are all AEs with PTs that fall under the scope of Narrow as indicated in Appendix 24.

6.1.19 New anti-cancer treatment

New anti-cancer treatments include medications, surgery and radiotherapy which started after the last dose of study drug (section 6.1.5.2). See section 23 for details on schedule of events for new anti-cancer therapies. As per protocol v14.0, new anti-cancer treatments are collected only for Arms 1, 2 and 3.

If pelabresib is permanently discontinued in a patient in Arm 2 and 3, but the patient is indicated for continued treatment of ruxolitinib at the discretion of the investigator, then this will be regarded as a new anti-cancer therapy.

6.2 Analysis Sets

6.2.1 Screened Patients Population Set

The screened patients population set will include all patients who have signed the informed consent form (ICF).

6.2.2 Intent-to-Treat Set (ITT)

The Intent-to-Treat (ITT) set will include all screened patients who have received at least 1 dose of any study treatment component.

6.2.3 Safety Analysis Set (SAF)

The safety set will include all screened patients who have received at least 1 dose of any study treatment component. Safety analyses will be performed on SAF.

6.2.4 Per-Protocol Analysis Set (PPS)

The per-protocol set (PPS) will include all patients who have received at least 1 dose of any study treatment component and who do not have any relevant protocol deviations. Protocol deviations that will lead to an exclusion from the PP set will be decided prior to database lock. All protocol deviations or conditions leading to exclusion from the PP set will be detailed during the protocol deviation review and documented. Sensitivity analyses of the primary and selected secondary endpoints will be performed using PPS in the population(s).

Beyond the definition above, the criteria indicated in the following document will also be applied for PPS:

- A2-DRM Meeting Minutes_MANIFEST_2Aug2023.pdf.

6.2.5 PK Analysis Set (PKAS)

The PK analysis set will include all patients in the ITT set who have received any amount of study drug and have evaluable PK data collected. For any further details on exclusion/inclusion into the PKAS, refer to the PK Analysis Plan.

6.2.6 Pharmacodynamic Analysis Set (PDAS)

The PDAS will include all patients in the ITT set who have received any amount of study drug and have evaluable pharmacodynamic data collected. Patients in the ITT set have evaluable pharmacodynamic data if at least 1 pre- and post-treatment record for Ct-IL-8, Ct-PPIB and Ct-B2M is available at any time throughout the study.

Beyond the definition above, the criteria indicated in the following document will also be applied for PDAS:

- NOTE_TO_THE_FILE_IMP_MIX_UP_site_51_FINAL.pdf

6.2.7 Planned Analyses for different Analyses sets

Table 1: Overview of the analyses performed on the different analysis sets for summary analyses

	Screened Patients Population	ITT	SAF	PPS	PKAS	PDAS
Disposition	Yes	Yes				
Protocol Deviation		Yes				
Baseline and Demographic		Yes				
Prior therapies and prior medications		Yes				
Medical History		Yes				
Concomitant Medications		Yes				
Exposure			Yes			
Efficacy Endpoints (primary, secondary and exploratory)		Yes		Yes (on primary and selected secondary endpoints)		
Subgroup Analysis		Yes		Yes (on primary and selected secondary endpoints)		
Adverse Event Summaries			Yes			
Laboratory values			Yes			
Vital Signs			Yes			
Deaths		Yes	Yes			
Pharmacodynamic Analysis						Yes
Pharmacokinetic Analysis					Yes	

7 Medical coding

Coding for adverse event, medical history and non-drug therapies will be performed using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or later, as applicable. Entries will be grouped by System Organ Class and Preferred Term.

All prior and concomitant medications collected from screening through the study period will be coded using the WHO Drug Dictionary Enhanced (WHO-DDE March 2021Format B3/C3 or later) and will be grouped by Anatomical Therapeutic Chemical (ATC) Level 4 class and preferred name.

The toxicity grade of AEs, the relationship of the event to study drug administration, and medical history are captured directly from eCRF. The toxicity grade of adverse events and medical history will be coded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) V4.03 or higher.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to the severity of mild, moderate, severe, life-threatening, and death. This grading system places a value on the importance of an event although there is not necessarily proportionality among grades (a grade 2 is not twice as bad as a grade 1).

8 General statistical rules

8.1 General principles of statistical programming and handling analysis dataset

The statistical analysis will be performed on the analysis study database with appropriate software, SAS® Software version 9.4 or above (SAS Institute, Cary, N.C.).

For submission purpose all the source data from eCRF is implemented to agree with Study Data Tabulation Model (SDTM) v1.4 dataset and SDTM implementation guide v3.2 or later.

8.2 Variable types and descriptive statistics

Descriptive statistics will be calculated according to the type of data as specified in sections 8.2.1, 8.2.2 and 8.2.3.

8.2.1 Categorical data

Categorical data will be summarized showing the number and percentage of patients within each category (patients with missing values will be counted in the denominator). The number and percentage of patients with missing data will also be provided. Where applicable, changes from baseline in the categorical data will be summarized using shift tables.

In case of subcategories, the relative frequencies will be calculated on the basis of the patients in the respective category, in which case a footnote will be added explaining the different denominators.

8.2.2 Continuous data

Continuous data (e.g., laboratory, vital signs, etc.) will be presented in the descriptive summary tables showing number of non-missing observations, number of missing observations, arithmetic mean, standard deviation (StD), minimum and maximum values, median and, unless otherwise specified, quartiles (Q1 and Q3).

If not otherwise specified, the following rules are applied:

- Percentages are presented to 1 decimal points.
- Percentage equal to 0 or 100 are presented as such without a decimal point.

- Ratios/Event rates are reported to 3 decimal points.
- The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place. In general, the maximum number of decimal places reported will be four for any summary statistic.

8.2.3 Duration of Time data

Unless otherwise specified, duration of time data will be analyzed using the method of Kaplan-Meier (K-M) (specifications provided in section 8.5.3 as well as - where applicable - for the relevant endpoint). In addition, where applicable, duration of follow-up time will be analyzed using the reverse K-M method.

Unless otherwise specified, duration of time data will be presented in weeks.

8.2.4 Incidence reporting (AE, CM, MH)

Unless differently specified, the number and percentage of patients, along with the event counts (for AE summary tables) will be reported in the summary tables of AEs, concomitant medications, and medical history. A patient will be counted only once if she/he comes across more than one time of the same AE/CM/MH event capturing the highest intensity/toxicity/worst outcome, etc., exceptions will be made for patients who experience an AE before the start of study drug and, later after the start of study drug, the AEs developed into higher intensity/toxicity/worst outcome. The AE and MH summary tables will be sorted in terms of decreasing frequency of overall group for system organ class (SOC) and the preferred term (PT) within SOC. The CM summary tables will be ordered in terms of decreasing frequency of ATC level and the preferred name within the ATC level.

8.3 Conventions

Unless otherwise specified, the following conventions will be applied to all analyses:

- 1 year = 365.25 days. Year is calculated as (days/365.25) rounded up to 1 significant digit,
- 1 month = 30.4375 days. Month is calculated as (days/30.4375) rounded up to1 significant digit,
- 1 pound = 0.454 kg,
- 1 inch = 2.54 cm,
- Time to event or duration of event endpoints will be based on the actual date rather than the associated visit date,
- Missing efficacy or safety data will not be imputed unless otherwise specified,
- For laboratory results collected as < or > a numeric value, 0.0000000001 will be subtracted or added, respectively, to the value,
- For safety analyses, percentages will be calculated based on the number of patients in the analysis population,

- For by-visit observed data analyses, percentages will be calculated based on the number of patients with non-missing data as the denominator unless otherwise specified.

8.4 Computing and Coding standards

Tables, Listings and Figures	SAS version 9.4 or higher
Coding	
Adverse Events	MedDRA version 23.0 or higher
Medical Histories	MedDRA version 23.0 or higher
Prior and Concomitant Medications	WHODrug version March 2021 Format B3/C3 or later
Grading	
Adverse Events	CTCAE Version 4.03 or later
Labs	CTCAE Version 4.03 or later

8.5 Analysis Methods

8.5.1 Center Pooling

Unless otherwise specified, data from all participating centers will be combined for the analyses.

8.5.2 Analysis of Binary data

All binary outcome variables of the study will be analysed descriptively; exact 95% confidence limits (using the Clopper-Pearson exact method, [2]) will be reported.

Response variables will be coded 1 for response and 0 for non-response.

8.5.3 Analysis of time-to-event endpoints

The following sections present a general methodology to be used to analyze time-to-event variables.

All time-to-event endpoints will be analyzed using the Kaplan-Meier methodology and results will be tabulated. In addition, a summary of the censoring reasons will be produced for all time-to-event endpoints. For the following time-to-event variables, the Kaplan-Meier method will also be displayed graphically:

- Time to conversion from TD to TI in patients who enroll as TD,
- Duration of RBC TI in patients who enroll as TD,
- Duration of the splenic response,
- Duration of treatment,
- Duration of follow-up time,
- Overall Survival.

Details for the K-M estimates and for the censoring strategy are presented in sections 8.5.3.1 and 8.5.3.2, respectively.

8.5.3.1 Kaplan-Meier estimates

The survival function will be estimated using the Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST in SAS. Median survival will be obtained along with 95% confidence limits. The confidence limits will be constructed using Brookmeyer and Crowley (1982) method, which is obtained from the conftype = linear option from PROC LIFETEST. K-M estimates and 95% confidence limits for the K-M estimate (calculated with Greenwood's formula) will be provided at specific time points. The K-M method will be tabulated and displayed graphically. Further details of the analysis are provided in the relevant analysis sections.

8.5.3.2 Censoring strategy for time-to-event endpoints

Depending on the time-to-event endpoint, the following censoring rules are defined and applied:

Endpoint	Situation	Date of Censoring/Event	Outcome	Censoring reason reported
Time to TD to TI conversion	Event: TD to TI conversion	Date of the event	Not censored	N.A.
	No event	Date of last contact (section 6.1.9)	Censored	Patient without TD to TI conversion
	Patient with no event who dies	Date of death	Censored	Death
	Patient with no event who discontinues the study prior to week 12	Date of last contact (section 6.1.9)	Censored	Discontinued study without TD to TI conversion.
Duration of RBC TI in patients who enroll as TD	Event: Loss of RBC TI	Date of the event	Not censored	N.A.
	Event: death	Date of death	Not censored	N.A.
	No event	Last contact date (see section 6.1.9)	Censored	Patient without event
	Patient who achieved TI discontinued the study and never received another transfusion	Last contact date (see section 6.1.9)	Censored	Discontinued the study without receiving any RBC transfusion from achievement of RBC TI.
Duration of early anemic response in patients who enroll as TD	Event: Loss of early anemic response	Date of event	Not censored	N.A.
	Event: death	Date of death	Not censored	N.A.

	No event	Last contact date (see section 6.1.9)	Censored	Patient without event
	Patient discontinues the study before week 8	Last contact date (section 6.1.9)	Censored	Discontinued the study without event
Time to early anemic response in patients who enroll as TD	Event: Early anemic response	Date of the event	Not censored	N.A.
	No event	Last contact date (section 6.1.9)	Censored	Patient without event
	Patient with no event who dies	Date of death	Censored	Death
	Patient discontinued the study before week 8	Last contact date (section 6.1.9)	Censored	Discontinued the study without event.
Duration of anemic response in patients who are non-TD at enrolment	Event: Loss of anemic response	Date of event	Not censored	N.A.
	Event: death	Date of death	Not censored	N.A.
	No event	Last contact date (see section 6.1.9)	Censored	Patient without event
	Patient discontinues the study before week 12	Last contact date (section 6.1.9)	Censored	Discontinued the study without event
Time to anemic response in patients who are non-TD at enrolment	Event: Anemic response	Date of the event	Not censored	N.A.
	No event	Last contact date (section 6.1.9)	Censored	Patient without event
	Patient with no event who dies	Date of death	Censored	Death
	Patient discontinued the study before week 12	Last contact date (section 6.1.9)	Censored	Discontinued the study without event.
Duration of overall Hematological Response	Event: Loss of Hematological Response	Date of the event	Not censored	N.A.
	Event: death	Date of death	Not censored	N.A.
	No event (Ongoing Response)	Last contact date (see section 6.1.9)	Censored	Patient without event

	Patient discontinues the study with no event	Last contact date (section 6.1.9)	Censored	Discontinued the study without event.
Duration of composite OHR and MPN-SAF TSS50 response	Event: Loss of response	Date of event	Not censored	N.A.
	Event: death	Date of death	Not censored	N.A.
	No event (Ongoing response)	Last contact date (see section 6.1.9)	Censored	Patient without event
	Patient discontinues the study with no event	Last contact date (section 6.1.9)	Censored	Discontinued the study without event.
Time to Overall Splenic Response	Event: Overall SVR35 Response	Date of event	Not censored	N.A.
	No event (No Response)	Last contact date (see section 6.1.9)	Censored	Patient without event
	Patient with no event who dies	Date of death	Censored	Death
	Patient discontinues the study with no event	Last contact date (section 6.1.9)	Censored	Discontinued the study without event.
Duration of Overall Splenic Response	See section 15.4.5	See section 15.4.5	See section 15.4.5	See section 15.4.5
Time to MFSAF TSS50	Event: TSS50 Response	Date of event	Not censored	N.A.
	No event (No Response)	Last contact date (see section 6.1.9)	Censored	Patient without event
	Patient with no event who dies	Date of death	Censored	Death
	Patient discontinues the study with no event	Last contact date (section 6.1.9)	Censored	Discontinued the study without event.
Duration of the MFSAF TSS50 response	Event: Loss of TSS50 response	Date of the event	Not censored	N.A.
	Event: Death	Date of death	Not censored	N.A.
	No event (Response Ongoing)	Date of last adequate MFSAF assessment: For patient with a TSS50, it is the date	Censored	Patient without loss of TSS50

		of the last available MFSAF assessment at which a loss of TSS50 is not observed.		
	Patient with TSS50 who discontinues the study prior to loss of TSS50	Date of last adequate MFSAF assessment: For patient with a TSS50, it is the date of the last available MFSAF assessment at which a loss of TSS50 is not observed.	Censored	Patient discontinued the study without loss of TSS50
	Patient with TSS50 receives a new anti-cancer treatment	Date of first dose of the new anti-cancer treatment	Censored	Initiation of new anti-cancer treatment
Duration of the MPN-SAF TSS50 response	Event: Loss of TSS50 response	Date of event	Not censored	N.A.
	Event: death	Date of death	Not censored	N.A.
	No event (Response ongoing)	Date of last adequate MPN-SAF assessment: For patient with a TSS50, it is the date of the last available MPN-SAF assessment at which a loss of TSS50 is not observed.	Censored	Patient without loss of TSS50
	Patient with TSS50 who discontinues from the study prior to loss of TSS50	Date of last adequate MPN-SAF assessment: For patient with a TSS50, it is the date of the last available MPN-SAF assessment at which a loss of TSS50 is not	Censored	Patient discontinued the study without loss of TSS50
Overall Survival	See section 15.8	See section 15.8	See section 15.8	See section 15.8
Duration of treatment	See section 14	See section 14	See section 14	See section 14
Duration of follow-up time	See section 14	See section 14	See section 14	See section 14

8.6 Data included in the analysis and cutoff date

The following steps will be performed for inclusion of data in a given analysis:

1. A data cutoff date will be identified by the Trial Statistician based on a timing of a given analysis as defined in section 5.2 and communicated to the CTT and the CRO team.
2. Data cutoff will be applied as described in the corresponding data cutoff plan.

9 Patient disposition

Disposition of patients will be summarized and listed for the screened patients population set and for the ITT set, separately. Data will be presented for each arm and overall. For Arms 1 and 2, data will also be presented by arm and cohort.

Patient disposition for the screened patients population set will include the following:

- Number and percentage of patients in the ITT set, the SAF, the PPS, and the PDAS;
- Number and percentage of screened patients by Country;
- Number and percentage of screened patients by the following age groups: 18-64 years, 65-84 years, 85 years and older.

Patient disposition for the ITT set will include the following:

- Number and percentage of patients in the ITT set by Country;
- Number and percentage of patients in the ITT set by the following age groups: 18-64 years, 65-84 years, 85 years and older;
- Number and percentage of patients in ITT set with inclusion criteria not met and/or exclusion criteria met;
- Number and percentage of patients who received at least one dose of CPI-0610;
- Number and percentage of patients who received at least one dose of ruxolitinib;
- Number and percentage of patients who received at least one dose of CPI-0610 and one dose of ruxolitinib;
- Number and percentage of patients who prematurely discontinued study treatment along with reason for treatment discontinuation (in eCRF page 'Subject Disposition - End of Treatment ');
- Number and percentage of patients who rolled over to the extension study (in eCRF page 'Subject Disposition - End of Study");
- Time since ICF signature expressed in weeks and calculated as detailed below:

Time since ICF signature (weeks) = (date of data cutoff/date of last contact - date of signature of ICF +1)/7

Note: for time since ICF signature, the date of data cutoff will be used for ongoing patients. If this is missing (e.g., a patient discontinues before the data cutoff date), the date of last contact will be used.

A listing of patients in the ITT set with inclusion criteria not met or/and exclusion criteria met will also be produced.

9.1 Duration on study and median follow-up time

Duration on study and median follow-up time will be analyzed on the ITT set.

Duration on study (in weeks) is defined as follows:

Duration on study (weeks): (date of EOS visit * - date of ICF signature +1)/7

*or date of death, whichever comes first.

Patients who discontinued from the study (i.e., who had an EOS visit) have an event with the date of the EOS visit. Patients who died also have an event, with the date of death as date of event.

Patients who are ongoing in the study at the cutoff date will be considered as censored with cutoff date as the censoring date (censoring reason: patient ongoing).

See section 21.2 for patients with EOS date < date of last contact.

Main analysis

Duration on study will be analyzed as detailed below. Data will be presented for each arm and overall. For Arms 1 and 2, data will also be presented by arm and cohort.

- The distribution of duration on study will be estimated using the Kaplan-Meier (K-M) method. The number of patients at risk and the number of patients censored will be summarized, together with the censoring reasons. K-M estimate (%) and 95% confidence limits for the K-M estimate (calculated with Greenwood's formula) will be provided at every 12 weeks and at EOS. Median, 25th and 75th percentile for survival time with 95% confidence limits, as well as first and last event occurred, will also be displayed. The confidence limits are constructed using Brookmeyer and Crowley (1982).
- Kaplan-Meier (K-M) method will be presented in tables and displayed graphically. The number of patients at risk, with event and censored will be displayed.

In addition, K-M estimate of duration of follow-up time (i.e., time on study as of data cutoff) will be provided. To summarize the follow-up time based on reverse K-M method, a K-M curve will be created where:

1. Patients who are ongoing at the cutoff date will be considered as "events", with cutoff date as the date of the event;
2. Patients who discontinued from the study (i.e., who had an EOS visit) and patients who died will be censored, with date of EOS visit and date of death, respectively, as the censoring date.

It will not be applicable for final analysis

Then, Q1, median, Q3 and their 95% confidence limits based on the KM estimates (using Brookmeyer and Crowley 1982 method) will be provided.

See section 8.5.3 for details on the production of the K-M estimate.

10 Protocol deviations (PDs)

Major PDs are listed and summarized displaying counts and percentages of patients in the ITT set with at least one major PD.

The PDs in the summary tables will be sorted by overall frequency, in descending order; if a tie occurs, the tied characteristics will be sorted alphabetically.

Major PDs will be described in a participant's listing.

Data will be presented for each arm and overall. For Arms 1 and 2, data will be presented by arm and cohort.

10.1 COVID-19 pandemic-related PDs

All protocol deviations in relation to COVID-19 will be identified based on reviews of the data prior to database lock.

The number and percentage of patients in the ITT set, with at least one protocol deviation (either major or minor) in relationship to COVID-19 will be summarized for each treatment arm and overall. For Arms 1 and 2, data will be presented by arm and cohort.

In addition, protocol deviations related to COVID-19 will be listed to describe the patient's information, treatment arm (and cohort, where applicable), exact item and date of protocol deviation. The listing will include a flag for major/minor PD.

10.2 PDs that lead to the exclusion from the PPS

PDs leading to the exclusion from the PPS will be summarized. A listing of patients excluded from the PPS will be provided as well. Data will be presented for each arm and overall. For Arms 1 and 2, data will be presented by arm and cohort.

A listing of inclusion/exclusion information on screened patients will also be presented. The listing will include whether all criteria were satisfied. For patients who did not satisfy with the criteria, the criteria number will be listed with the deviation.

11 Baseline, demographic and disease characteristics

Analyses will be performed on the ITT analysis set.

Table 2 below lists the demographic variables and the baseline disease characteristics that will be summarized. The descriptive summary will also include the proportion of missing data.

A listing of the demographic and baseline disease characteristics will also be presented.

Data will be presented for each arm and overall. For Arms 1 and 2, data will be presented by arm and cohort.

Table 2: Demographic and baseline disease characteristics

Continuous Variables:	**Summary Type**
Age at ICF signature (years)	Descriptive statistics (N, mean, standard deviation [SD], minimum and maximum values and quartiles (median, Q1 and Q3).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (Kg/m^2)	
Hemoglobin (g/dL)	
Platelet Count (10^9/L)	
Spleen Volume (cm^3)	
Spleen length (cm)	
Total Symptom Score*	
Time since diagnosis (months)	
Time of prior JAKi treatment (months)	
Duration of previous Hydroxyurea use (months)	
Categorical Variables	
Sex (male, female)	Frequency distribution with the number and percentage of patients in each category.
Race**	
Ethnicity	
Myelofibrosis Subtype ([Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, Post-Essential Thrombocythemia Myelofibrosis)]	
ECOG Performance Status*** [(0, 1, 2, ≥3)]	
Hemoglobin Group [(<10 g/dL, ≥10 g/dL)	
Platelet Count Group [(< 450 10^9/L, ≥ 450 10^9/L)	
Baseline Platelet Count [(≤ 200 10^9/L, > 200 10^9/L)]	
Mutation Status:	

Triple Negative [(Y, N)] *HMR* [(ASXL1, EZH2, IDH1, IDH2, SRSF2, U2AF1) Driver Mutations [(CALR, MPL, JAK2V617F)]	
Dynamic International Prognostic Scoring System [(Intermediate-1 risk, Intermediate-2 risk, High risk)]	
International Prognostic Scoring System [(Intermediate-1 risk, Intermediate-2 risk, High risk)]	
Previous hydroxyurea use (Yes/No/Missing)	
Prior JAKi treatment (yes/no)	

* Total Symptom Score as assessed using the MFSAF v4.0 and the MPN-SAF (depending on arm) in the corresponding eCRF page.

** If more than one races/ethnic origins have been chosen for a particular patient, it will be categorized as 'Other' in the tabulation and listed as 'Other:' with concatenated items for that patient.

*** ECOG at screening in the ECOG Performance Status eCRF page.

Notes to Table 2:

-Whenever hemoglobin is in g/dL, g/dL will be derived from SI unit for hemoglobin - i.e., g/L. To obtain g/dL, divide the value in g/L by 10.

- For Previous Hydrohyurea use (Yes/No/Missing), the following preferred terms will be considered: "Hydroxyurea", "Hydroxycarbamide".

- If age is missing, it will be derived in years as follows:

Age (years): (date of ICF signature - date of birth +1)/365.25

where, if the date of birth is partial, this will be imputed based on the imputation rules as provided in section 21.5.

- Spleen length (cm) will be presented for patients with palpable spleen length. The proportion of patients with non-palpable spleen length, as well as missing data will be presented, too. Patients with non-palpable spleen length are patients for whom the question "Palpable?" is answered as "N" in the eCRF page "Hepatic and Splenic Measurements by Palpation". Spleen length at baseline is the last non-missing assessment on or before C1D1 considering records collected both for palpable and for non-palpable spleen length - i.e., both assessments for palpable and non-palpable spleen length will be checked to determine baseline for this parameter and, among these, the latest record on or before C1D1 will be considered as baseline.

- See section 25 for the derivation rules for Mutation Status subgroups.

Time since diagnosis

Time since diagnosis is defined as the time from the date of diagnosis to the date of the informed consent signature, and is computed in months as follows:

Time since diagnosis (months) = (date of informed consent - date of diagnosis + 1)/ 30.4375

Where the date of the informed consent is collected in the Informed Consent eCRF page, and the date of diagnosis is derivable from the relevant data collected in the "Cancer History (CH)" eCRF page - i.e., "date of initial diagnosis (Day)", "date of initial diagnosis (Month)", and "date of initial diagnosis (Year)".

See section 21.5.1 for imputation rules for missing/incomplete dates of initial MF/ET diagnosis.

Prior JAKi treatment and Time of prior JAKi treatment

Prior JAKi treatment and Time of prior JAKi treatment are applicable for Arms 1, 2 and 4; they are not applicable for Arm 3 (i.e., JAKi Naïve patients).

Time of prior JAKi treatment is defined as the time from the start of prior JAKi treatment to the end date of prior JAKi treatment. For patients with an ongoing JAKi treatment at start of study, time of prior JAKi treatment is defined as the time from the start of prior JAKi treatment to C1D1 (section 6.1.6).

Time of prior JAKi treatment is computed in months as follows:

Time of prior JAKi treatment (months) = (end date of prior JAKi treatment - start date of prior JAKi treatment +1)/ 30.4375

and for patients with and ongoing JAKi treatment at start of study:

Time of prior JAKi treatment (months) = (date of C1D1 - start date of prior JAKi treatment + 1)/30.4375

See section 21.4 for handling of missing/partial dates of start/end of prior JAKi treatment.

Duration of previous hydroxyurea use (months)

Duration of previous hydroxyurea use is defined as the time from the start to the end date of prior hydroxyurea. For patients with an ongoing hydroxyurea use at start of study, duration is defined as the time from start of prior hydroxyurea use to C1D1 (section 6.1.6).

Duration of previous hydroxyurea use is computed in months as follows:

Duration of previous hydroxyurea use (months) = (end date of prior hydroxyurea - start date of prior hydroxyurea + 1)/ 30.4375

and for patients with ongoing hydroxyurea use at start of study:

Duration of previous hydroxyurea use (months) = (date of C1D1 - start date of prior hydroxyurea + 1)/ 30.4375

See section 21.4 for handling of missing/partial dates of start/end of prior hydroxyurea use.

Note: for time of prior JAKi treatment and for duration of previous hydroxyurea use, if the patient has multiple records for prior JAKi/prior hydroxyurea, the record with the earliest start date will be considered for the computation.

International Prognostic Scoring System (IPSS)

IPSS categories (i.e., Intermediate-1 risk, Intermediate-2 risk, High risk) will be derived from data on the Dynamic International Prognostic Scoring System (DIPSS), as collected in the eCRF page "Dynamic International Prognostic Scoring System (DIPSS)".

For each patient, the IPSS score will be derived. Afterwards, the patient will be assigned to the relevant IPSS category [4]. Details for the derivation are provided in what follows.

The DIPSS eCRF page collects 5 items (i.e., prognostic variables) that can be marked as "Yes/No":

1. Age > 65 years
2. Leukocyte count >25 x 10^9/L
3. Hemoglobin <10 g/dL
4. Circulating blast cells ≥1%
5. Constitutional symptoms

Each item marked as "Yes" contributes 1 risk factor and is assigned 1 point. For each patient, the IPSS score is obtained by summing the number of risk factors (i.e., the number of items marked as "Yes"), with a possible score that may range from 0 to 5.

The IPSS prognostic categories are obtained as displayed in the table below:

IPSS score derived	IPSS Risk Category
0	Low
1	Intermediate-1 risk
2	Intermediate-2 risk

≥3	High risk

Subgroup Analysis

(1) The set of demographic and baseline disease characteristics as reported in Table 2 above will be summarized (separately for demographic vs. baseline disease characteristics) descriptively on the following 3 sugroups of patients in the ITT set for all arms:

- Patients who experienced Transformation to Blast Phase throughout the study;
- Patients who experienced Accelerated Phase throughout the study*;
- Patients who experienced Transformation to Blast Phase or Accelerated Phase throughout the study.

Separate summay tables will be generated for each of the 3 subgroups. See sections 15.6.1 (Arms 1-3) and 15.6.2 (Arm 4) for specifications related to these subgroups of patients.

*Note: consistently with sections 15.6.1 and 15.6.2, these are patients who experienced Accelerated Phase and did not experience Transformation to Blast Phase throughout the study.

11.1 Prior Therapies and prior medications

Prior therapies and prior medications (see section 6.1.10 for definition) will be tabulated, separately, based on the ITT set. Prior therapies and prior medications will be summarized, separately, by ATC level 4 and PT. The summary for prior therapies will display data overall and by prior JAKi treatment subgroup (yes/no). Listings will also be provided.

Note: prior JAKi treatment subgroup is applicable only for Arm 1.

Data will be presented for each arm and overall. For Arms 1 and 2, data will be presented by arm and cohort.

For Arms 1 and 2, JAKi prior therapies and/or JAKi prior medications reported as ongoing by the date of C1D1 will be listed. The listing will include JAKi prior therapies and/or prior medications that result as ongoing at C1D1, where ongoing at C1D1 means the start date of the JAKi therapy/medication < C1D1 and the end date >= C1D1 or missing.

12 Medical history

Medical history and current medical conditions will be summarized by SOC, preferred term and by intensity grade. In addition, current medical conditions will be separately tabulated. Data will be presented based on the ITT set.

Notes:

- Medical history is defined as records in the "Medical History/Baseline Signs and Symptoms (MH)" eCRF page which are not ongoing (i.e., the checkbox for question 2.R.6 "Is it ongoing?" is ticked "NO" in the eCRF page).
- Current medical conditions are defined as records in the "Medical History/Baseline Signs and Symptoms (MH)" eCRF page which are ongoing (i.e., the checkbox for question 2.R.6 "Is it ongoing?" is ticked "YES" in the eCRF page).

A listing on medical history and current medical conditions will be provided.

Data will be presented for each arm and overall. For Arms 1 and 2, data will be presented by arm and cohort.

13 Non-Study Medications and non-drug therapies

13.1 Concomitant Medications

Concomitant medications (see definition in section 6.1.10) will be tabulated based on the ITT set. Data will be presented for each arm and overall. For Arms 1 and 2, data will be presented by arm and cohort. The following will be provided:

- The number and percentage of patients who took at least one medication will be summarized. The summary will be presented by Anatomic Therapeutic Chemical (ATC) class (level 4) and PT within each ATC class. ATC classes will be sorted by descending order. If the frequencies of ATC classes are the same, then alphabetical order will be used. The same rule applies for preferred term within ATC class.
  Patients who took the same medication more than once (as qualified by the same PT(s)) are counted only once. In case the reported medication is assigned to several PTs, patients are counted for each individual PT.
- A listing of concomitant medications will also be produced.

13.2 New Anti-cancer therapies

New anti-cancer therapies will be summarized, by arm/cohort, for Arms 1, 2 and 3. The summary will include the following:

- Number and percentage of patients in the ITT set who received at least 1 new anti-cancer therapy.
- Number and percentage of patients in the ITT set who received at least 1 new anti-cancer therapy by type of therapy (i.e., including medications, surgery and radiotherapy).

A listing will also be produced. Not applicable for Arm 4.

14 Study treatment exposure and dose

14.1 Duration of Exposure to study treatment and median follow-up time

For each of the study treatment components, treatment duration (in weeks) is defined as follows:

For CPI-0610:

Treatment duration (weeks) = (date of last dose of CPI-0610 - date of first dose of CPI-0610 + 1)/7

Patients who had a last dose of CPI-0610 have an event with the date of last dose as the event date. Patients who are ongoing at the cutoff date will be considered as censored with cutoff date as the censoring date (censoring reason: patient ongoing. It will be not applicable for final analysis).

For ruxolitinib:

Treatment duration (weeks) = (Date of last dose of ruxolitinib - date of first dose of ruxolitinib + 1)/7

The date of the last dose of ruxolitinib will be considered as the event date. If patient discontinues ruxolitinib within 30 days after CPI-0610 last dose, ruxolitinib last dose date will be considered as the event date. If, at last dose of CPI-0610 + 30 days, the patient is on treatment for ruxolitinib, the patient will be censored at last dose of CPI-0610 + 30 days (censoring reason: Patient on treatment for ruxolitinib). Patients who are ongoing at the cutoff date will be censored at date of data cutoff (censoring reason: Patient ongoing. It will be not applicable for final analysis).

Furthermore, in Arms 2 and 3 only, the duration of the combination treatment (i.e., concomitant exposure to both CPI-0610 and ruxolitinib) will be evaluated. This is defined as the time from first to last concomitant administration of CPI-0610 and ruxolitinib, and is computed in weeks as follows:

Combined treatment duration (weeks) =

(Date of last concomitant intake - Date of first concomitant intake +1) / 7

Where the dates of first and last concomitant intake are, respectively, the first and last day in which the patient is administered both CPI-0610 and ruxolitinib.

The date of the last concomitant intake of CPI-0610 and ruxolitinib will be considered as the event date. This may occur under the following situations:

- The patient had an EOT visit, independently on whether or not still on treatment with ruxolitinib;
- The patient discontinues at least 1 of the treatment components or both for any reason.

If at the date of data cutoff the patient is still on the combined treatment, the date of data cutoff will be used as the censoring date (censoring reason: Patient ongoing. It will be not applicable for final analysis).

Main analysis

For each individual study treatment component (i.e., CPI-0610/ruxolitinib), as well as for the combined treatment (i.e., CPI-0610 + ruxolitinib), treatment duration will be analyzed on the SAF as detailed below. The duration of the combined treatment will be analyzed only for arms 2 and 3.

- The distribution of treatment duration will be estimated using the Kaplan-Meier (K-M) method. The number of patients at risk and the number of patients censored will be summarized, together with the censoring reasons. K-M estimate (%) and 95% confidence limits for the K-M estimate (calculated with Greenwood's formula) will be provided at every 12 weeks and at EOT. Median, 25th and 75th percentile for survival time with 95% confidence limits, as well as first and last event occurred, will also be displayed. The confidence limits are constructed using Brookmeyer and Crowley (1982).

In addition, K-M estimate of duration of follow-up time (i.e., time on treatment as of data cutoff) will be provided. To summarize the follow-up time based on reverse K-M method, for each component of the study treatment and for the combination treatment, a K-M curve will be created where:

1. Patients who are ongoing with CPI-0610/ruxolitinib/CPI-0610 + ruxolitinib at the cutoff date will be considered as "events" with cutoff date as the date of the event;
2. For CPI-0610, patients with a last dose of CPI-0610 are censored with the date of the last dose as the censoring date.
3. For patients who discontinue ruxolitinib:
    - If ruxolitinib discontinuation occurs within 30 days after CPI-0610 last dose, the date of ruxolitinib last dose will be the censoring date. If, at last dose of CPI-0610 + 30 days, the patient is on treatment for ruxolitinib, the patient will be censored at last dose of CPI-0610 + 30 days.
4. For combined treatment:
    - Patients with a date of last concomitant intake of CPI-0610 and ruxolitinib (as defined above) will be censored with their date of last concomitant intake.
    - Patients who discontinued treatment because of death will be censored at last contact date.

It will not be applicable for final analysis.

Then, Q1, median, Q3 and their 95% confidence limits based on the KM estimates (using Brookmeyer and Crowley 1982 method) will be provided.

See section 8.5.3 for details on the production of the K-M estimate.

Subgroup Analysis

For each individual study treatment component (i.e., CPI-0610/ruxolitinib), as well as for the combined treatment (i.e., CPI-0610 + ruxolitinib), the same Kaplan-Meier analysis as described for the main analysis above will be conducted by the following subgroups:

– Gender (Male, Female);

– Race*;

- Myelofibrosis Subtype (Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, Post-Essential Thrombocythemia Myelofibrosis) (not applicable for Arm 4);
- Hemoglobin Group (<10 g/dL, ≥10 g/dL);
- Baseline Platelet Count Group (≤ 200, > 200, < 450, ≥ 450);
- Driver Mutations (CALR, MPL, JAK2V617F);
- Dynamic International Prognostic Scoring System (Intermediate-1 risk, Intermediate-2 risk, High risk);
- International Prognostic Scoring System (Intermediate-1 risk, Intermediate-2 risk, High risk).

* If more than one race has been chosen for a particular patient, it will be categorized as 'Other'.

See section 11 for further details on the subgroups above.

K-M estimate of duration of follow-up time based on the reverse Kaplan-Meier method will not be generated for the by-subgroup analysis of exposure to study treatment component.

14.2 Compliance to study treatment components

For each component of study treatment, compliance expresses the amount of drug administered per unit of time compared to the planned amount of drug as per protocol. Compliance (mg) is defined as follows:

Compliance (mg) = Actual Cumulative Dose (mg) / Planned Cumulative Dose (mg)

Where:

(1) The **Actual Cumulative Dose (mg)** for each component of the study treatment is obtained by summing up the actual daily doses* for each cycle as entered in the eCRF pages (see details below) until the last administration of each component of the study treatment.

Note: ruxolitinib is administered BID, and the dose collected in the eCRF page is the planned total daily dose (i.e., BID), the actual total daily dose will be derived as follows:

- if one of the AM or PM dose is skipped for a given day (i.e., the response to question "Check if not administered" is ticked for a given day of administration in the eCRF page), it will be assumed that the AM and PM doses constitute half of the planned total daily dose. Accordingly, the actual total daily dose for that day will be obtained by dividing the planned total daily dose by 2.

For each day of each cycle, information on actual daily doses of CPI-0610 is collected in the following eCRF page: "CPI-0610 Admin (14-Days Daily Dosing) - Phase 2 (DA_15)", field = "Dose taken (mg)".

For each day of each cycle, information on the planned total daily dose of ruxolitinib as well as on ruxolitinib AM/PM dosing administration is collected in the following eCRF pages for ruxolitinib dosing administration .

(2) The **Planned Cumulative Dose (mg)** for each component of the study treatment and arm is defined in Table 3 below:

Table 3: Computation of Planned Cumulative Dose (mg) by arm and study treatment component

	Planned Cumulative Dose (mg) for each Study Treatment component	
Arm	**Ruxolitinib**	**CPI-0610**
1	N.A.	[Starting dose at C1D1 x (14 days)] + [dose at C2D1 x(n.cycles from C2 to last cycle x 14 days)]* *Starting dose for arm 1 = 125 mg QD. CPI-0610 can be uptitrated from Cycle 2 Day 1 based on the criteria outlined in protocol.
2	Starting dose x (n. cycles x 21 days)	[Starting dose at C1D1 x (n 2 cycles x14 days)] + [dose at C3D1 x(n.cycles from C3 to last cycle x 14 days)]* *Starting dose for arm 2 = 125 mg QD. CPI-0610 can be uptitrated from Cycle 3 Day 1 based on the criteria outlined in protocol.
3	[starting dose x (n. 2 cycles x 21 days)] + [dose at C3D1 x (n. cycles from C3 to last cycle + 1)]* Where n. cycles= number of available cycles. *Ruxolitinib dose is uptitrated if the clinical conditions as specified in Table 7 of the protocol are observed.	[starting dose x (n. 4 cycles x 14 days)] + [dose at C5D1 x (n. cycles from C5 to last cycle x 14 days)] *Starting dose at C1D1 = 125 mg QD; CPI-0610 can be uptitrated from Cycle 5 Day 1 based on the criteria outlined in protocol.
4	N.A.	Starting dose* x (n. cycles x 14 days) *starting dose for arm 4= 225 mg QD.

To compute the planned cumulative dose by cycle, the following will be applied:

	Planned Cumulative Dose (mg) by cycle for each Study Treatment component	
Arm	**Ruxolitinib**	**CPI-0610**
1	N.A.	For cycle 1:

2	Starting dose x 21(days). *Note*: Since ruxolitinib is administered BID, the starting dose at CnD1 will be the total daily dose at CnD1.	Starting dose at C1D1* x 14(days) From cycle 2 onward*: Starting dose at CnD1 x 14(days) *Starting dose for arms 1 and 2: For cycle 1 =125 mg QD; From cycle 2 onward: ≥ 125mg QD. CPI-0610 can be uptitrated in patients who are not progressing and who meet the upward titration criteria starting from Cycle 2 Day 1 (Monotherapy Arm [Arm 1]) or Cycle 3 Day 1 (Combination Arm [Arm 2]).
3	For cycle 1 and cycle 2: Starting dose * 21(days) From cycle 3 onward*: Starting dose at C3D1 * 21(days) *Ruxolitinib dose is uptitrated at cycle 3 if the clinical conditions as specified in Table 7 of the protocol are observed.	For cycles 1 to 4: Starting dose* x 14(days) From cycle 5 onward: Starting dose at C5D1* x 14(Days) *Starting dose for arm 3: For cycle 1 =125 mg QD; From cycle 5 onward: ≥ 125mg QD. CPI-0610 can be uptitrated from Cycle 5 Day 1 based on the criteria outlined in protocol.
4	N.A.	Starting dose* x 14(days) *starting dose for arm 4= 225 mg QD.

Note: for the computation of the planned dose by cycle for CPI-0610, if for a given cycle, the dose is missing, the dose at the previous cycle will be used.

Unless otherwise specified, the following will be analysed for each component of the study treatment:

- Separate descriptive summaries will be provided for compliance and actual cumulative dose. The summaries will be presented by cycle and overall. The summaries will be generated for each arm and overall. For arms 1 and 2, data will be presented by arm and cohort.
- For ruxolitinib only, a frequency distribution of starting dose will be provided, with number and percentage of patients in each of the following categories:

  - 10 mg BID
  - 15 mg BID

- 20 mg BID
- 30 mg BID
- 40 mg BID
- 50 mg BID

The summaries will be generated for each arm and overall; data for arm 2 will be presented by cohort.

For each of the study treatment components, a listing for compliance to study treatment components will be generated as well.

14.2.1 Doses Titrations

For all arms:

- CPI-0610 doses titrations from C1D1 up to C35D1: a shift table will be produced presenting the number and percentage of patients in each category (i.e., C1D1 and CnD1) with regards to the categories of CPI-0610 daily dosage. The categories of CPI-0610 daily dosage include:

  - 50 mg
  - 75 mg
  - 100 mg
  - 125 mg
  - 150 mg
  - 175 mg
  - 200 mg
  - 225 mg

  Where: CnD1 is day 1 of each cycle following cycle 1; and the actual daily dose of CPI-0610 at day 1 of each cycle will be used to assign patients to the dosage categories listed above and generate the shift table.

- CPI-0610 doses titrations from C1D1 to the maximum dose received: the same shift table as above will be produced presenting number and percentage of patients in the categories of CPI-0610 dosage at C1D1 vs. maximum dose received. The same categories of CPI-0610 daily dosage as listed above will be used.

- CPI-0610 doses titrations from C1D1 to the minimum dose received: the same shift table as above will be produced presenting number and percentage of patients in the categories of CPI-0610 dosage at C1D1 vs. minimum dose received. The same categories of CPI-0610 daily dosage as listed above will be used.

For arms 2 and 3:

- Ruxolitinib doses titrations from C1D1 to C35D1: a shift table will be produced presenting the number and percentage of patients in each category (i.e., C1D1 and CnD1) with regards to the categories of ruxolitinib total daily dosage. The categories of ruxolitinib total daily dosage include:

- 5 mg
- 10 mg
- 15 mg
- 20 mg
- 25 mg
- 30 mg
- 35 mg
- 40 mg
- 45 mg
- 50 mg

Where: CnD1 is day 1 of each cycle following cycle 1; and the actual total daily dose of Ruxolitinib at day 1 of each cycle will be used to assign patients to the dosage categories listed above and generate the shift table.

- Ruxolitinib doses titrations from C1D1 to the maximum dose received: the same shift table as above will be produced presenting number and percentage of patients in the categories of Ruxolitinib dosage at C1D1 vs. maximum dose received. The same categories of Ruxolitinib total daily dosage as listed above will be used.

- Ruxolitinib doses titrations from C1D1 to the minimum dose received: the same shift table as above will be produced presenting number and percentage of patients in the categories of Ruxolitinib dosage at C1D1 vs. minimum dose received. The same categories of Ruxolitinib total daily dosage as listed above will be used.

The analyses above will be generated for each arm and overall; data for arms 2 and 3 will be presented by cohort.

Note: the shift tables above may display other shift categories for the dose titrations of both CPI-0610 and ruxolitinib in addition to those listed, should there be patients with titration patterns not included in the categories listed above.

14.2.2 Compliance to study treatment components as prescribed by the investigator

For each component of study treatment, compliance as prescribed by the principal investigator (PI) expresses the amount of patients' drug intake per unit of time compared to the planned amount of drug as prescribed by the PI. Compliance to study treatment components (%) as prescribed by the PI is defined as detailed in what follows.

Compliance as prescribed by the PI (%) =

[(actual cumulative dose (mg) / prescribed planned cumulative dose (mg)) * 100]

Where:

(1) For the Actual Cumulative Dose (mg), see definitions and derivations of the Actual Cumulative Dose in section 14.2.

(2) The Planned Cumulative Dose as prescribed by the PI (mg) for each study treatment component and arm is defined in Table 3. 1 below.

Table 3. 1: Computation of Planned Cumulative Dose (mg) as Prescribed by the Principal Investigator

	Planned Cumulative Dose (mg) as prescribed by the PI for each Study Treatment component	
Arm	CPI-0610	Ruxolitinib
1, 2, 3, 4	The planned cumulative dose as prescribed by the PI is the sum of the planned dose prescribed by the PI for each of the patients' available cycles. Where: The planned dose as prescribed by the PI for a cycle is derived as follows: (Planned daily dose for the cycle (mg)* x 14 days) *Question 1 in eCRF page "CPI-0610 Admin (14-days Daily Dosing) - Phase 2 (DA_15): *Planned daily dose for this cycle (mg).*	For Arms 2 and 3 only: The planned cumulative dose as prescribed by the PI is the sum of the planned dose prescribed by the PI for each of the patients' available cycles. Where: The planned dose as prescribed by the PI for a cycle is derived as follows: (Planned total daily dose for the cycle (mg)* x 21 days) * Field *Planned total daily dose of Ruxolitinib for this cycle (mg)* in the ruxolitinib dosing administration eCRF pages.

Notes to Table 3. 1:

- If, for a patient, the planned daily dose for the cycle as per eCRF page is missing or equal to 0 mg for a given cycle, that cycle will not be included in the computation of compliance as prescribed by the investigator. This means that, irrespective of the (un)availability of the actual dose for that cycle, the planned cumulative dose as prescribed by the PI will not include the prescribed planned dose for the cycle at stake. Consequently, the cycle actual dose will not be included in the computation of compliance either. For the sake of clarity, two examples are given in scenarios A and B below.

Scenario A:

For a patient with 6 cycles, the prescribed planned daily dose for cycles 2 and 4 is missing/0 mg and the actual dose is available for all 6 cycles.

- The planned cumulative dose as prescribed by the PI for this patient will be computed as:

  [(planned dose as prescribed by the PI at cycle 1) + (planned dose as prescribed by the PI at cycle 3) + (planned dose as prescribed by the PI at cycle 5) + (planned dose as prescribed by the PI at cycle 6)]

- The actual cumulative dose for this patient will be computed as:

  [(actual daily doses at cycle 1) + (actual daily doses at cycle 3) + (actual daily doses at cycle 5) + (actual daily doses at cycle 6)]

- Compliance as prescribed by the PI will be obtained as per the definition of compliance provided above, whereby cycles 2 and 4 are excluded from the computations.

Scenario B:

For a patient with 6 cycles, the prescribed planned daily dose for cycles 2 and 4 is missing/0 mg and the actual dose for cycles 2 and 4 is also missing. Because of the unavailability of the prescribed daily dose at cycles 2 and 4, the same steps as illustrated in scenario A above apply.

Additional notes

For CPI-0610:

1) If a patient has unscheduled doses of CPI-0610 within the same cycle such that dosing for that cycle > 14 days, these unscheduled doses will be counted in the computation of the actual dose for that cycle (hence also in the computation of the actual cumulative dose). For example, if at cycle 30 a patient has 14 days of 125 mg CPI-0610 intake + 3 unscheduled intakes of 125 mg each, the patient's actual dose for that cycle will be 125mg x 17 days (the patient's planned dose will still be computed as PI's prescribed planned dose x 14 days).

2) If for a given cycle, a patient's intakes of CPI-0610 are all recorded as 'Not done' and there are unscheduled intakes of CPI-0610 within that cycle, the cycle compliance as prescribed by the PI will be computed based on the unscheduled records. For example, at cycle 30, a patient has 14 days of CPI-0610 marked as 'Not done'. The patient also has 14 unscheduled records of CPI-0610 within the same cycle .In such a case, the PI's prescribed compliance for the patient's cycle 30 will be based on the 14 unscheduled records.

For ruxolitinib:

1) For discontinued patients: if a patient has completed the last available cycle and, after this, unscheduled intakes of ruxolitinib are recorded, the unscheduled intakes will be considered as the patient's last completed cycle +1, and:

a) Compliance as prescribed by the PI will therefore be computed also for the patient's last completed cycle +1.

b) The computation of the planned cumulative dose as prescribed by the PI as well as the actual cumulative dose will include the patient's last completed cycle+1.

For example, if a discontinued patient's last completed cycle is cycle 30, and after this the patient has some unscheduled doses of ruxolitininb, the unscheduled intakes will be considered as a cycle 31 for this patient. Consequently the PI's prescribed compliance for a cycle 31 will be computed.

2) If a patient has unscheduled doses of ruxolitinib within the same cycle such that dosing for that cycle > 21 days, these unscheduled doses will be counted in the computation of the actual dose for that cycle (hence also in the computation of the actual cumulative dose). For example, if at cycle 30 a patient has 21 days of 20 mg (i.e., total daily dose) of ruxolitinib intake + 3 unscheduled days of ruxolitinib 20 mg each, the patient's actual dose for that cycle will be 20mg X 24 days (while the planned dose still will consider 21 days).

The following will be analysed for each component of the study treatment:

- Separate descriptive summaries will be provided for compliance as prescribed by the PI and actual cumulative dose. The summaries will be presented by cycle and overall. The summaries will be generated for each arm and overall. For arms 1 and 2, data will be presented by arm and cohort.
- For ruxolitinib only, a frequency distribution of starting total daily dose will be provided, with number and percentage of patients in each of the following categories:

  - 10 mg
  - 15 mg
  - 20 mg
  - 30 mg
  - 40 mg
  - 50 mg

- Data on compliance as prescribed by the PI will be listed.

Note: to compute the cycle-wise compliance as prescribed by the investigator, the rule for the planned dose as prescribed by the PI for a cycle (Table 3. 1) will be used. If, for a given cycle, the planned dose as prescribed by the PI is missing/0 mg, compliance to the PI's prescribed dose for that cycle will not be computed and the patient will be excluded for the analysis of compliance for that cycle.

14.2.3 Relative dose intensity

For each of the study treatment components, overall relative dose intensity, overall relative dose intensity up to Cycle 8 and relative dose intensity by cycle will be analysed.

Overall relative dose intensity is defined as follows:

Overall relative dose intensity (mg) = actual dose intensity (mg) / expected dose intensity (mg)

Where, for each component of the study treatment:

(1) The **actual dose intensity (mg)** is obtained by dividing the actual cumulative dose (mg) (see section 14.2) by the actual cumulative number of days of a patient's cycles (i.e., actual cumulative dose / actual cumulative number of days of cycles). The actual cumulative number of days of a patient's cycles is the

number of days between the start date of the first cycle and the end date of the last available cycle, and is computed as (end date of last cycle - start date of cycle 1 +1)* .

*Note: if a patient has only 1 cycle, the number of days for that cycle will be set to the per-protocol planned number of days in a cycle.

(2) The **expected dose intensity (mg)** is obtained by dividing the planned cumulative dose (mg) (see section 14.2) by the expected number of days of a patient's cycles (i.e., planned cumulative dose (mg) / expected cycles days). The expected number of days of a patient's cycles is the per-protocol number of days from C1D1 to day 21 of a patient's last cycle and is computed as (n. cycles from C1 to last cycle x 21 days).

Overall relative dose intensity up to Cycle 8:

This is the overall relative dose intensity up to Cycle 8 (included) and is obtained by computing the overall dose intensity as described above up to cycle 8.

Where, for each component of the study treatment:

(1) The **actual dose intensity (mg) up to Cycle 8** is obtained by dividing the actual cumulative dose (mg) (see section 14.2) up to cycle 8 by the actual number of days up to Cycle 8. The latter is computed as (end date of cycle 8 - start date of cycle 1 +1). For patients with less than 8 cycles of treatment, the end date of cycle 8 will be replaced with the end date of the last available cycle, unless the patient has only 1 cycle. In which case, the number of days for that cycle will be set to the per-protocol planned number of days in a cycle.

(2) The **expected dose intensity (mg) up to Cycle 8** is obtained by dividing the planned cumulative dose (mg) (see section 14.2) up to Cycle 8 (see below) by the expected number of days up to Cycle 8. The latter is the per-protocol number of days from C1D1 to day 21 of Cycle 8 and is computed as (n. 8 cycles x 21 days). For patients with less than 8 cycles of treatment, the expected number of days is computed as (n. cycles from C1D1 to last cycle x 21 days).

Planned cumulative dose up to Cycle 8:

The planned cumulative dose up to Cycle 8 is computed based on Table 3 (section 14.2), and adapted accordingly to consider only n. 8 cycles. Therefore, for example for the planned cumulative dose in Arm 2, the computation in Table 3 will be adapted as follows:

	Planned Cumulative dose (mg) for each study treatment component in Arm 2	
	Ruxolitinib	CPI-0610
Overall Planned cumulative dose (mg) - Extract from Table 3	Starting dose x (**n. cycles** x 21 days)	[Starting dose at C1D1 x (n 2 cycles x14 days)] + [dose at C3D1 x(n.cycles from C3 **to last cycle** x 14 days)]

Planned cumulative dose (mg) up to Cycle 8	Starting dose x (**n. 8 cycles** x 21 days)	[Starting dose at C1D1 x (n 2 cycles x14 days)] + [dose at C3D1 x(n.cycles from C3 **to C8** x 14 days)]

For patients with less than 8 cycles, the last available cycle will be taken into account.

Relative dose intensity by cycle (mg):

For each study treatment component, relative dose intensity by cycle is obtained as (actual dose intensity for each cycle / expected dose intensity of each cycle).

Where, for each study treatment component:

(1) The **actual dose intensity for each cycle (mg)** is obtained by dividing the actual cumulative dose (mg) (see section 14.2) for each cycle by the actual number of days in that cycle. The actual number of days in each cycle is computed as (cycle end date - cycle start date + 1). If a patient has only 1 cycle, the actual number of days in that cycle will be set to the per-protocol number of days in a cycle.

(2) For each study treatment component, the expected dose intensity for each cycle (mg) is obtained by dividing the cycle-wise planned cumulative dose (mg) (see section 14.2) by the expected number of days in a cycle (i.e., n. 21 days).

Separately for each component of the study treatment, the following will be analysed:

- Separate descriptive summaries will be provided for Overall relative dose intensity, Relative dose intensity up to Cycle 8 and relative dose intensity by Cycle. For cycle-wise relative dose intensity, only cycles up to Cycle 8 will be presented. The summaries will be generated for each arm and overall. For arms 1 and 2, data will be presented by arm and cohort. Overall relative dose intensity, relative dose intensity up to Cycle 8 and relative dose intensity by cycle will be expressed in percent, obtained by multiplying each of the above (mg) by 100.

Supportive and Additional Analysis

1) Relative Dose Intensity II

An additional analysis of relative dose intensity will be conducted in which the expected dose intensity will be computed based on the planned dose as prescribed by the principal investigator (section 14.2.2). Therefore, for each of the study treatment components, overall relative dose intensity, overall relative dose intensity up to Cycle 8 and relative dose intensity by cycle will be analysed based on the definitions provided in what follows.

The same *Additional notes* as provided in section 14.2.2 for the PI's prescribed compliance are applicable here as well, if needed for the computation of actual dose intensity and/or expected dose intensity as prescribed by the PI.

A. Overall relative dose intensity (mg) =

actual dose intensity (mg) / expected dose intensity as per PI's prescription (mg)

Where:

(1) Actual dose intensity (mg): see definition above for the analysis of relative dose intensity.

(2) Expected dose intensity as per PI's prescription (mg): is obtained by dividing the PI's prescribed planned cumulative dose (mg) (section 14.2.2) by the expected number of days of a patient's cycles (i.e., PI's prescribed planned cumulative dose (mg) / expected cycles days).

(3) If the PI's prescribed planned dose for a given cycle is missing/0 mg, hence the PI's prescribed planned dose for that cycle is excluded from the computation of the PI's prescribed planned cumulative dose, the cycle in question will be excluded also from the computation of the actual dose intensity.

B. Overall relative dose intensity up to Cycle 8 =

actual dose intensity up to Cycle 8 (mg) / expected dose intensity up to Cycle 8 (mg) as per PI's prescription

Where:

(1) Actual dose intensity up to Cycle 8 (mg): see definition above for the analysis of relative dose intensity.

(2) Expected dose intensity up to Cycle 8 (mg) as per PI's prescription: is obtained as specified above for the expected dose intensity as per PI's prescription and adapted to include cycles up to Cycle 8 (inclusive) (i.e., the PI's prescribed planned cumulative dose up to Cycle 8 will be the sum of the PI's prescribed planned doses for cycles 1-to-8).

(3) The same specification for missing/0mg PI's prescribed planned dose as above applies here, too.

C. Relative dose intensity by cycle (mg) =

actual dose intensity for each cycle (mg) / expected dose intensity for each cycle (mg) as per PI's prescription

Where:

(1) Actual dose intensity for each cycle (mg): see definition above for the analysis of relative dose intensity.

(2) Expected dose intensity for each cycle (mg) as per PI's prescription: is obtained by dividing the cycle-wise PI' s prescribed planned dose (section 14.2.2) by the expected number of days in a cycle (i.e., n. 21 days).

The same analysis as described for Relative Dose Intensity will be conducted for Relative Dose Intensity II (i.e., relative dose intensity based on the PI's prescribed planned dose).

14,3 Dose reductions, interruptions or permanent discontinuations

Dose reduction

A dose reduction is defined as any decrease in dose from the protocol planned dose of each study treatment component.

For CPI-0610, information of dose reductions is captured in the "CPI-0610 Admin (14-Days Daily Dosing) - Phase 2 (DA_15)" eCRF page. For ruxolitinib, dose reductions data are collected in the "ruxolitinib dosing administration eCRF pages.

Dose interruption

A dose interruption is defined as any dose skipped within a given cycle.

For CPI-0610, information on dose interruptions are collected in the "CPI-0610 Admin (14-Days Daily Dosing) - Phase 2 (DA_15)" eCRF page, under question 4.1.2 ("Not Done").

For ruxolinib, information on dose interruption is captured in the Ruxolitinib Dosing Administration-Combination Arm (RXH_1) eCRF page, under questions 4.1.2, 4.2.2, etc., depending on the day of administration. If both AM and PM doses for a given day are skipped, these will be considered as dose interruption. If only an AM or PM dose of the same day is skipped, this will be considered as a dose interruption.

See section 21.6 for imputation of dates for dose interruption.

For each component of study treatment, the following will be summarized:

- Number and percentage of patients with dose reduction, along with the reasons for dose reduction and a descriptive summary of the time to first dose reduction (see details below).
- Total number of dose reductions;
- Cumulative duration of dose reductions (see details below).
- Number and percentage of patients with dose interruptions, along with the reasons for dose interruptions and a descriptive summary of the time to first dose interruption (see details below).
- Total number of dose interruptions;
- Cumulative duration of dose interruptions (see details below).

Note: for the total number of dose reductions, any decrease in dose will be counted as a dose reduction. For example, suppose a patient has the dosage pattern below for CPI-0610 during the treatment, where the numbered list below corresponds to progressive modification in time of dosage:

1. 125 mg
2. 100 mg
3. 50 mg
4. 100 mg
5. 50 mg
6. 25 mg

The total number of dose reductions in the example above is 4 (at points (2), (3), (5) and (6)).

However, if for a patient there is no dose re-escalation after a dose reduction and the dosage remains unchanged up to the last available intake, this will count as one reduction. For example, based on the dosage pattern below, the total number of dose reductions is 2:

1. 125 mg
2. 100 mg
3. 50 mg
4. 50 mg
5. 50 mg
6. 50 mg.

The summaries will be generated for each arm and overall. For arms 1 and 2, data will be presented by arm and cohort. Data for CPI-0610 will be summarized for all arms. Data for Ruxolitinib will be summarized for arms 2 and 3. Data for the cumulative duration of dose reductions/interruptions will be presented in weeks.

The time to first dose reduction and dose interruption is computed as detailed below.

For CPI-0610:

Time to first dose reduction = (date of CPI-0610 dose reduction - date of first dose of CPI-0610 +1)/7

Time to first dose interruption= (date of CPI-0610 dose interruption- date of first dose of CPI-0610 +1)/7

For Ruxolitinib:

Time to first dose reduction = (date of ruxolitinib dose reduction - date of first dose of ruxolitinib +1)/7

Time to first dose interruption = (date of ruxolitinib dose interruption- date of first dose of ruxolitinib +1)/7

Cumulative duration of dose reductions/interruptions

This is the cumulative duration of all dose reductions/interruptions that occur from start of treatment (i.e., from the first available intake of study treatment component) to end of treatment (i.e., last available intake of study treatment component). Further details are specified in what follows.

Cumulative duration of dose reductions

First, the duration of each dose reduction will be computed at detailed below for each of the study treatment components. Afterwards, the cumulative duration will be obtained by summing up the duration for each occurrence of dose reduction/interruption.

The duration of each CPI-0610/ruxolitinib dose reduction is computed in weeks as follows:

- (Date of first CPI-0610/ruxolitinib dose re-escalation after a dose reduction - date of CPI-0610/ruxolitinib dose reduction + 1)/7

Notes:

- a dose re-escalation is an increase in dosage after a reduction. For example, after 125 mg of CPI-0610 daily intake, the dosage is reduced to 75 mg, a dose re-escalation is the first subsequent dose > 75mg.

- if, after a dose reduction, there is no dose re-escalation and the dosage remains reduced up to the last available intake, then the date of the last available intake will be used instead of the date of the dose re-escalation in the formula above.

Cumulative duration of dose interruptions

This is derived based on the following approach:

- For CPI-0610: every dose interrupted (with respect to the per-protocol planned administration of the drug - i.e., once a day for the first 14 days of a cycle, see section 6.1.4) is considered as 1 day of interruption. The cumulative duration of the interruptions is the sum of the days in which the dose is interrupted. For example, if a patient interrupts CPI-0610 60 times while on treatment, the number of the doses interrupted will be equal to 60, and the cumulative duration of dose interruptions will be equal to 60 days.
  To obtain the cumulative duration in weeks, divide by 7 the sum of the days in which the dose is interrupted.

- For ruxolitinib: the same rationale as detailed above for CPI-0610 is adopted. Therefore, the cumulative duration of dose interruptions is the sum of days in which the dose is interrupted; where the sum of the days is based on the number of doses skipped.
  Note:
  Since ruxolitinib is administered BID:
  - If both the AM and the PM doses on the same day are skipped (i.e., 'Not done'), this will count as 1 day of interruption).
  - If only the AM or the PM dose is skipped on the same day, this will be considered as half a day of interruption. For example, if a patient skips the PM doses from day 15 to day 21 of a cycle, the duration of this interruption will be equal to 3.5 days - i.e., (day 21 - day 15 +1)/2.

In addition, dose reductions and interruptions due to AEs will be investigated. The following will be summarized, separately for each study treatment component:

For dose reduction due to AEs:

- Number and percentage of patients with dose reductions due to AEs;
- Time to first dose reduction due to AEs;
- Cumulative duration of dose reductions due to AEs;
- Number and percentage of patients with dose reduction due to AEs and subsequent dose re-escalation (computed over patients with dose reduction due to AEs);
- Total number of dose reductions due to AEs.

For dose interruption due to AEs:

- Number and percentage of patients with dose interruptions due to AEs;
- Time to first dose interruption due to AEs;
- Cumulative duration of dose interruptions due to AEs;
- Number and percentage of patients with dose interruption due to AEs and who restarted the treatment afterwards (computed over patients with dose interruption due to AE).
- Total number of dose interruptions due to AEs.

Where:

For time to first dose reduction/interruption due to AE:

adapt the computation of time to first dose reduction/interruption as detailed above. For example, time to first CPI-0610 dose reduction due to AE will be computed as (date of CPI-0610 dose reduction due to AE - date of first dose of CPI-0610 +1)/7.

For cumulative duration of dose reductions/interruptions due to AEs:

This is the cumulative duration of all dose reductions/interruptions due to AEs that occur from start of treatment (i.e., first intake of study treatment components) to end of treatment (i.e., last available intake of study treatment components).

First, the duration of each dose reduction/interruption due to AEs will be computed as detailed below for each of the study treatment components. Afterward, the cumulative duration will be obtained by summing up the duration for each occurrence of dose reduction/interruption.

The duration of each CPI-0610/ruxolitinib dose reduction due to AEs is computed in weeks as follows:

- (Date of first CPI-0610/ruxolitinib dose re-escalation after a dose reduction due to AEs - date of CPI-0610/ruxolitininb dose reduction due to AE + 1)/7

Note: a dose re-escalation is an increase in dosage after a reduction.

The cumulative duration of CPI-0610/ruxolitinib dose interruption due to AEs is derived based on the computational steps as detailed below:

- Step 1: for each adverse event leading to a dose interruption, select the start and end date of this event to first identify the interval of time based on which computing the duration of a dose interruption.
- Step 2: within the interval of time as identified in step (1), count the total number of doses interrupted and derive in days the duration of the interruption as follows:
    - For CPI-0610: every dose interrupted (with respect to the per-protocol planned administration of the drug - i.e., once a day for the first 14 days of a cycle, see section 6.1.4) is considered as 1 day of interruption. For each dose interruption due to AEs during the study, the duration of the interruption is the sum of the days in which the dose is interrupted. For example, if a patient has an AE leading to CPI-0610 interruption from day 3 to day 9 of a cycle, the number of the doses interrupted will be equal to 7, and the duration of this interruption will be equal to 7 days. If a patient has an AE leading to CPI-0610 interruption from - say - day 12 of cycle 3 to day 7 of cycle 4, the

number of the doses skipped for this patient will be equal to 10 (i.e., days 12-to-14 in cycle 3 + days 1-to-7 in cycle 4) and the duration of this interruption will correspond to a total of 10 days. In other words, the per-protocol 7-day break of CPI-0610 administration for each cycle is excluded from the computation of the duration of dose interruption due to AEs.

- For ruxolitinib: the same rationale as detailed above for CPI-0610 is adopted, exception made for the per-protocol 7-day break that is not applicable to ruxolitinib (see 6.1.4). For each dose interruption due to AEs during the study, the duration of the interruption is the sum of days in which the dose is interrupted; where the sum of the days is based on the number of doses skipped within the interval of time as per step (1). If - within the interval of time of each AE leading to ruxolitinib interruption, a patient interrupts both the AM and the PM doses of ruxolitinib on the same day, this will count as 1 day of interruption.
  Note: in the context of an interruption due to an AE, it is not usual case with ruxolitinib that only the AM or PM dose on the same day is skipped because the total daily dose can be either interrupted or reduced (if reduced, this is still administered BID). However, in the unusual case that only the AM or the PM dose is skipped due to an AE, this will be considered as half a day of interruption. For example, if a patient has an AE from day 15 to day 21 of a cycle and skips the PM doses in this interval of time, the total duration of this interruption will be equal to 3.5 days - i.e., (day 21 - day 15 +1)/2.

- Step 3: the cumulative duration of the dose interruptions due to AEs throughout the study will be the sum of the duration of each interruption as detailed above, and will be computed in weeks by dividing by 7 the sum of the days for all doses interruptions.

For patients with dose reduction due to AEs and subsequent dose re-escalation:

These are patients with at least 1 dose reduction due to AEs and for whom the dose was increased after a dose reduction.

15 Efficacy analysis

All efficacy analyses will be presented based on the ITT set. Selected efficacy endpoints will be also presented based on the PPS.

A listing of patients excluded from the main analysis of each efficacy evaluation as described below will be produced. This listing will be generated for the ITT set and will specify the efficacy endpoint the patient was excluded from, as well as the reason for the exclusion.

Unless otherwise specified, all efficacy data will be presented for each applicable arm/cohort and overall. For Arms 1 and 2, data will be presented by arm and cohort.

15.1 Response criteria

Efficacy assessments for arms 1, 2 and 3 are made according to the revised International Working Group-Myeloproliferative Neoplasm Research and Treatment (IWG-MRT) response criteria for Myelofibrosis. These are described in detail in section 7.2.4.5, Table 29 of the protocol. For arm 4, efficacy assessments are made according to the European LeukemiaNet (ELN) response criteria for essential thrombocythemia and polycythemia vera [3].

15.2 Transfusion Independence Analysis

15.2.1 Conversion rate from TD to TI in patients who enroll as TD

15.2.1.1 Definition

This is the primary endpoint for cohorts 1A and 2A, CCI [redacted]

The conversion rate from TD to TI is defined as the proportion of patients who converted from transfusion dependence (TD) to transfusion independence (TI), where:

TD is defined as: having received ≥ 6 units of RBC transfusion during the 12 weeks prior to dosing (i.e., an average of ≥2 units of RBC transfusion per month in the 12 weeks prior to dosing).

TI is defined as absence of RBC transfusions in any interval of 12 weeks from start of treatment to end of treatment*.

*Note: where start of treatment is the date of first administration of study drug (section 6.1.5.1); and end of treatment is:

For ongoing patients: the date of last administration of study drug (section 6.1.5.2);

For discontinued patients: the date of treatment discontinuation as reported in the "Subject Disposition - End of Treatment (DS)" eCRF page.

15.2.1.2 Analysis

Arm/Cohort: cohorts 1A and 2A; CCI

Main analyses

For cohorts 1A and 2A CCI [redacted] the following will be presented:

a. The number and percentage of patients in the ITT set for cohorts 1A and 2A CCI [redacted]
b. The number and percentage of patients in the ITT set for cohorts 1A and 2A CCI [redacted]
c. The number and percentage of patients who converted from TD to TI will be summarized; exact 95% confidence limits of the binomial distribution will be provided.

(c) above will be based on (a). Patients without post-dose RBC transfusion (at any time from start of treatment to end of treatment) will be considered as TD to TI conversion responders. Early discontinued patients prior to week 12 will be considered as non-responders.

A listing of transfusions will be generated as well.

Sensitivity Analysis for main analyses:

(1) A sensitivity analysis for the conversion rate from TD to TI will be conducted. This consists in applying the following definition of TD:

- Patients are defined as TD based on the response to question (1) in the transfusion history screening eCRF page: "Is the subject transfusion dependent?". If question (1) is answered as "yes", then the patient will be considered as TD. If it is answered as "no", then the patient will be considered as non-TD.

The same analysis as described for main analysis above will be conducted.

(2) For Cohorts 1A and 2A only: the same analysis as described for main analysis above will be conducted on the PPS analysis set.

Subgroup Analysis:

(1) The rate of conversion from TD to TI in patients who enroll as TD, as defined in section 15.2.1.1, will be summarized by the subgroup categories as specified Table 7 - section 15.4.1.2.

For each subgroup, the following will be provided:

a. The number and percentage of patients in the ITT set for cohorts 1A and 2A CCI [redacted]

b. The number and percentage of patients who converted from TD to TI (based on (a) above) will be summarized; exact 95% confidence limits of the binomial distribution will be provided. Patients without post-dose RBC transfusion (at any time from start of treatment to end of treatment) will be considered as TD to TI conversion responders. Early discontinued patients prior to week 12 will be considered as non-responders.

15.2.2 CCI [redacted]


CCI

15.2.3 Duration of RBC TI in patients who enroll as TD

15.2.3.1 Definition

This is a secondary endpoint for cohorts 1A and 2A, CCI

Duration of RBC TI is defined as the longest duration of RBC TI for patients who achieved TI ≥ 12 weeks during the treatment period (week 1-24, week 1-48, during the entire study treatment period).

The duration of RBC TI is first computed in weeks as follows:

- (Date of the first occurrence of RBC transfusion after TI –onset date of TI +1)/7

Afterwards, the longest duration of RBC TI is selected for the analysis.

For discontinued patients who have achieved RBC TI (having ≥ 12 weeks RBC transfusion free) and never received another RBC transfusion during the course of the study, the duration of TI will be censored at the last contact date. For ongoing patients who have achieved RBC TI and never received another transfusion throughout the study, the duration of TI will be censored at the last contact date. See section 8.5.3.2 for details on censoring strategy, and section 6.1.9 for the definition of date of last contact.

15.2.3.2 **Analysis**

Arm/Cohort: cohorts 1A and 2A; arm 3.

Main analysis

The duration of RBC TI in patients who enroll as TD will be analyzed as follows:

- The following will be provided:

  a) The number and percentage of patients in the ITT set for cohorts 1A and 2A and arm 3 enrolled as TD and who achieved TI;

- The number and percentage of patients with event and number of patients with censoring (based on (a) above) along with reasons for censoring will be summarized.
- The distribution of the duration of RBC TI will be estimated using the K-M method. K-M estimate (%) and 95% confidence limits for the K-M estimate (calculated with Greenwood's formula) will be provided at every 12 weeks and at EOT. Median, 25th and 75th percentile for survival time with 95% confidence limits will also be displayed. The confidence limits are constructed using Brookmeyer and Crowley (1982).
- Kaplan-Meier (K-M) method will be presented in tables and displayed graphically. The number of patients at risk, with event and censored will be displayed.

See sections 8.5.3.1 and 8.5.3.2 for details for the K-M estimates and for the censoring strategy and reasons, respectively.

In addition, the following will be provided:

- K-M estimate of follow-up time for the duration of RBC TI in patients who enroll as TD will be computed, where:
  - Patients who achieved RBC TI and subsequently had a loss of RBC TI are censored with their date of loss of RBC TI as the censoring date.
  - Patients who die are censored with the date of death as the censoring date.
  - Patients who are censored in the analysis of duration of RBC TI in patients who enroll as TD are considered as events. Therefore:

    Ongoing patients who achieved TI but without subsequent loss of RBC TI = event, with date of last contact (section 6.1.9) as the date of the event.

    Patients who achieved TI discontinued the study, and never received any RBC transfusion from achievement of RBC TI = event, with date of last contact as the date of the event.

Then, Q1, median, Q3 and their 95% CI based on the KM estimates (using Brookmeyer and Crowley 1982 method) will be provided.

The reverse K-M statistics will be computed over the number and percentage of patients in the ITT set for cohorts 1A and 2A and arm 3 who enrolled as TD and who achieved TI (i.e., (a) above). The analysis will be presented in table and displayed graphically.

Sensitivity analysis for main analysis

A sensitivity analysis for the duration of RBC TI in patients who enroll as TD will be conducted by applying the same definition of TD as the one for sensitivity analysis (1) for the conversion rate from TD to TI (section 15.2.1.2, *Sensitivity Analysis for main analyses*).

The same analysis as described for main analysis will be conducted.

Subgroup analysis

The following subgroup analyses will be provided:

(1) The duration of RBC TI in patients who enroll as TD will be analysed by the subgroup categories as specified Table 7 - section 15.4.1.2. The same Kaplan-Meier analysis as specified for the main analysis above will be conducted, with the following exception:

- No K-M estimate (%) will be provided at baseline nor every 12 weeks or at EOT. Only median, 25th and 75th percentile for survival time with 95% confidence limits (constructed using Brookmeyer and Crowley, 1982) will be presented.
- The K-M method will only be summarized in tables (i.e., no graph for the KM curve will be displayed).

Supportive and additional analysis

(1) Non-KM based analysis of duration of RBC TI in patients who enroll as TD and who achieved RBC TI

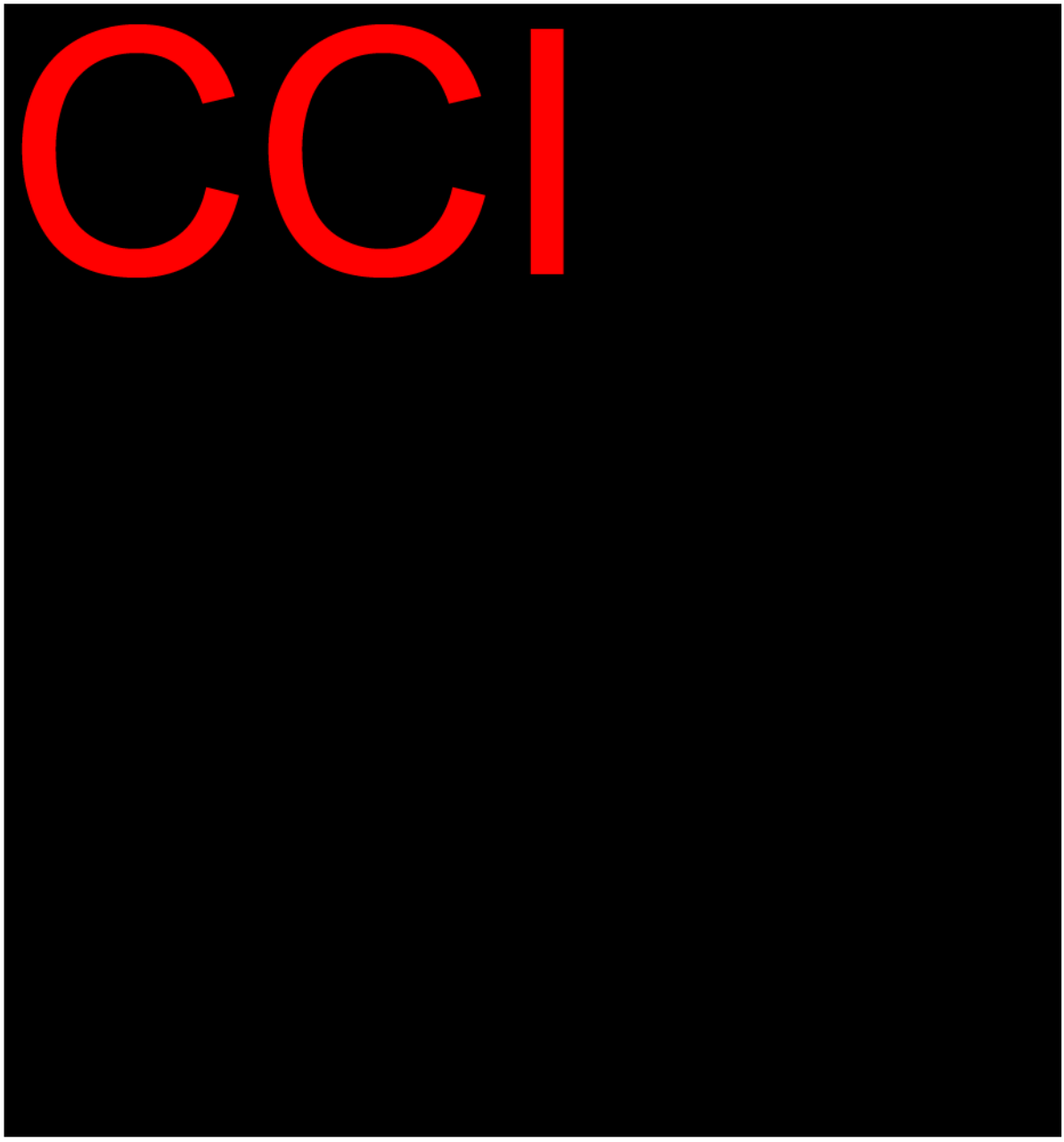
The duration of RBC TI in patients who enroll as TD will be summarized by means of descriptive statistics for patients who achieved RBC TI. Data will be presented for each of cohort 1A, cohort 2A and Arm 3, as well as overall.

See: section 15.2.3.1 for the definition of duration of RBC TI in patients who enroll as TD and section 15.2.1 for further definitions/specifications relevant to this endpoint. In addition, for the purpose of this analysis, duration of RBC TI will be computed in weeks as specified in the table below, depending on the situation. Note that the table below provides the formula for the computation of duration of RBC TI in weeks depending on several scenarios. After this, the longest duration of RBC TI will be selected for the analysis, as per definition in section 15.2.3.1.

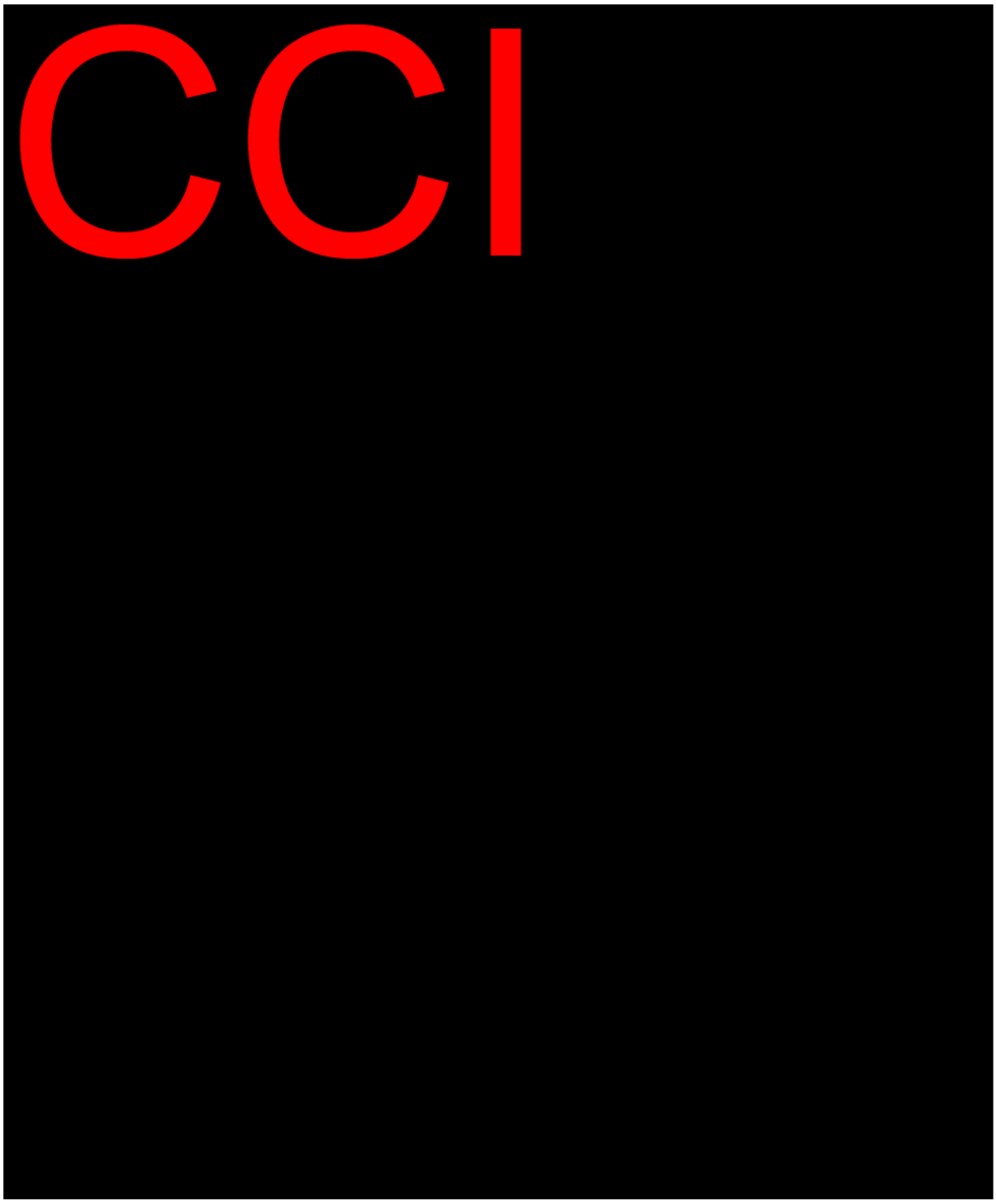
Non-KM based computation of duration of RBC TI in patients who enroll as TD and who achieve TI

Situation	Computation of duration of RBC TI (weeks)
Patient with achievement of RBC TI who subsequently lost RBC TI	See section 15.2.3.1.
Patient with achievement of RBC TI who dies	(Date of death - onset date of TI + 1) / 7.
Ongoing or discontinued patient with achievement of RBC TI who does not lose RBC TI	(last contact date - onset date of TI + 1) / 7.

15.2.4 CCI




CCI



15.3 Hematological Response Analysis

15.3.1 Early anemic response rate in patients who enroll as TD

15.3.1.1 Definition

This is a secondary endpoint for cohorts 1A and 2A; CCI [redacted]

The early anemic response rate is defined as the proportion of patients who achieve a ≥ 1 g/dL average increase (after applying the 14/3 day rule, see details below) from baseline in any 8-week mean hemoglobin concentration, as calculated over any rolling 8-week (56 days) period post-baseline in the absence of RBC transfusions during the treatment period and up to the latest Hgb assessment for each patient.

14/3-Day rule:

Only Hgb values that are collected at least 14 days after a transfusion may be used, unless there is another transfusion within 3 days after the Hgb assessment. If this occurs, the Hgb value prior to the second transfusion may be used (despite being <14 days after the previous transfusion). See section 6.1.15 for details on baseline definition after applying the 14/3-day rule.

See section 15.2.1.1 for the definition of TD at enrolment. See section 6.1.15 for baseline definition of early anemic response. See sections 22.4 and 22.6 for details on analysis visit windows and on unscheduled visits, respectively. See section 21.1 for handling of missing data.

Note:

For the selection of valid Hgb assessments (i.e., in light of the 14/3-day rule) for the derivation of early anemic response the following specifications apply:

- rolling 8-week (i.e., 56 days) intervals will be identified - e.g., 0-56 days, 1-57 days, 2-58 days;
- within the rolling 8-week intervals, only intervals without transfusions are eligible for the analysis;
- once any 8-week interval in the absence of any transfusion is identified, the 14/3-day rule will be applied and only Hgb assessments consistent with this will be considered as valid for the analysis.
- For the selection of the valid post-baseline Hgb assessments for early anemic response, only the 14 days constraint of the 14/3-day rule above is applicable.
- In addition, for the selection of valid Hgb assessments, the following apply:
    - If a Hgb assessment is collected exactly 14 days after a transfusion (i.e., on day 14 after a given transfusion), this Hgb assessment is not valid for the analysis.
    - If there is a Hgb assessment on the same day of a transfusion, this Hgb assessment will be valid for the analysis based on the assumption that Hgb is assessed prior to the transfusion. However, if the time of the transfusion and the Hgb assessment is available, then the time of the assessment will be used for the eligibility of the Hgb assessment, and only Hgb assessments collected earlier than the transfusion (based on time of collection) will be valid for the analysis.

15.3.1.2 **Analysis**

Arm/Cohort: cohort 1A, cohort 2A, arm 3.

Main analysis

Early anemic response will be analyzed as detailed below.

- The following will be provided:
    a. The number and percentage of patients in the ITT set for cohorts 1A and 2A and arm 3 who enrolled as TD;
    b. The number and percentage of patients in the ITT set for cohorts 1A and 2A and arm 3 who did not enroll as TD.
- The number and percentage of patients achieving early anemic response throughout the study will be summarized, along with exact 95% confidence limits for the binomial distribution. This will be computed over (a) above. Early discontinued patients before week 8 will be considered as non-responders.
- A summary of mean Hgb distribution by cycle will be provided (see sections 6.1.4 and 23 for treatment cycle definition and for details on the by-cycle assessments, respectively). Patients with non-missing baseline will be included in this summary even if the post-baseline assessments are not available. The summary will also show the number and percentage of missing data at baseline as well at each post-baseline assessment.
- The distribution of Hgb by cycle for the following subgroups of patients will be included in the summary above as separate tabs:

    - Baseline Hgb < 10 g/dL
    - Baseline Hgb ≥ 10 g/dL

- The distribution of Hgb by cycle and by baseline Hgb subgroups (see above) by cycle will also be presented graphically using boxplots.

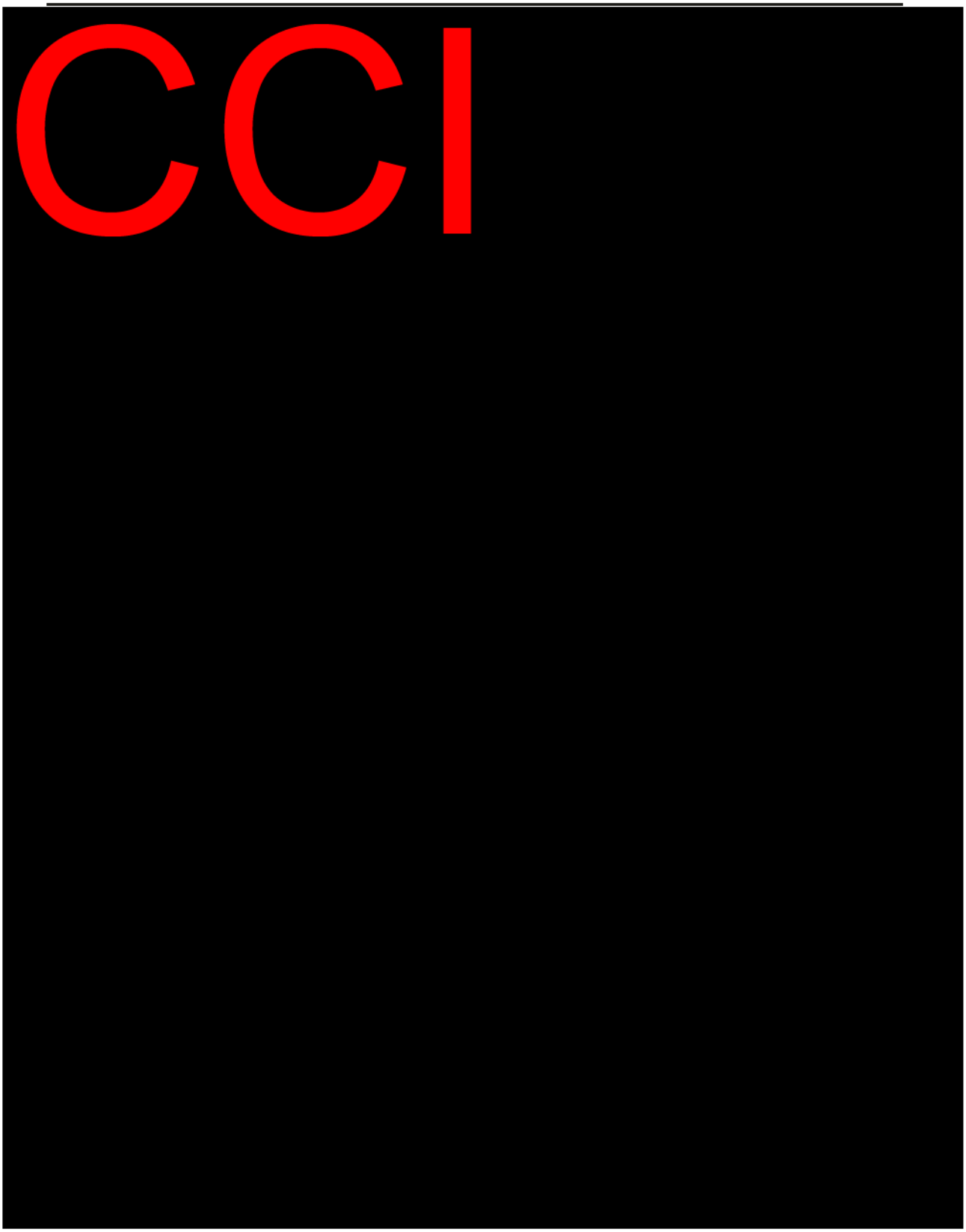
Note: Hgb in g/dL will be derived from the Hgb values in SI unit (i.e., g/L). To obtain g/dL, Hgb value in g/L will be divided by 10.

See section 6.1.15 for the definition of baseline for early anemic response. See sections 22.4 and 22.6 for, respectively, visit windows definition and unscheduled visits. See section 21.1 for imputation rules for early anemic response.

15.3.2 CCI [redacted]

CCI [redacted]

CCI [redacted]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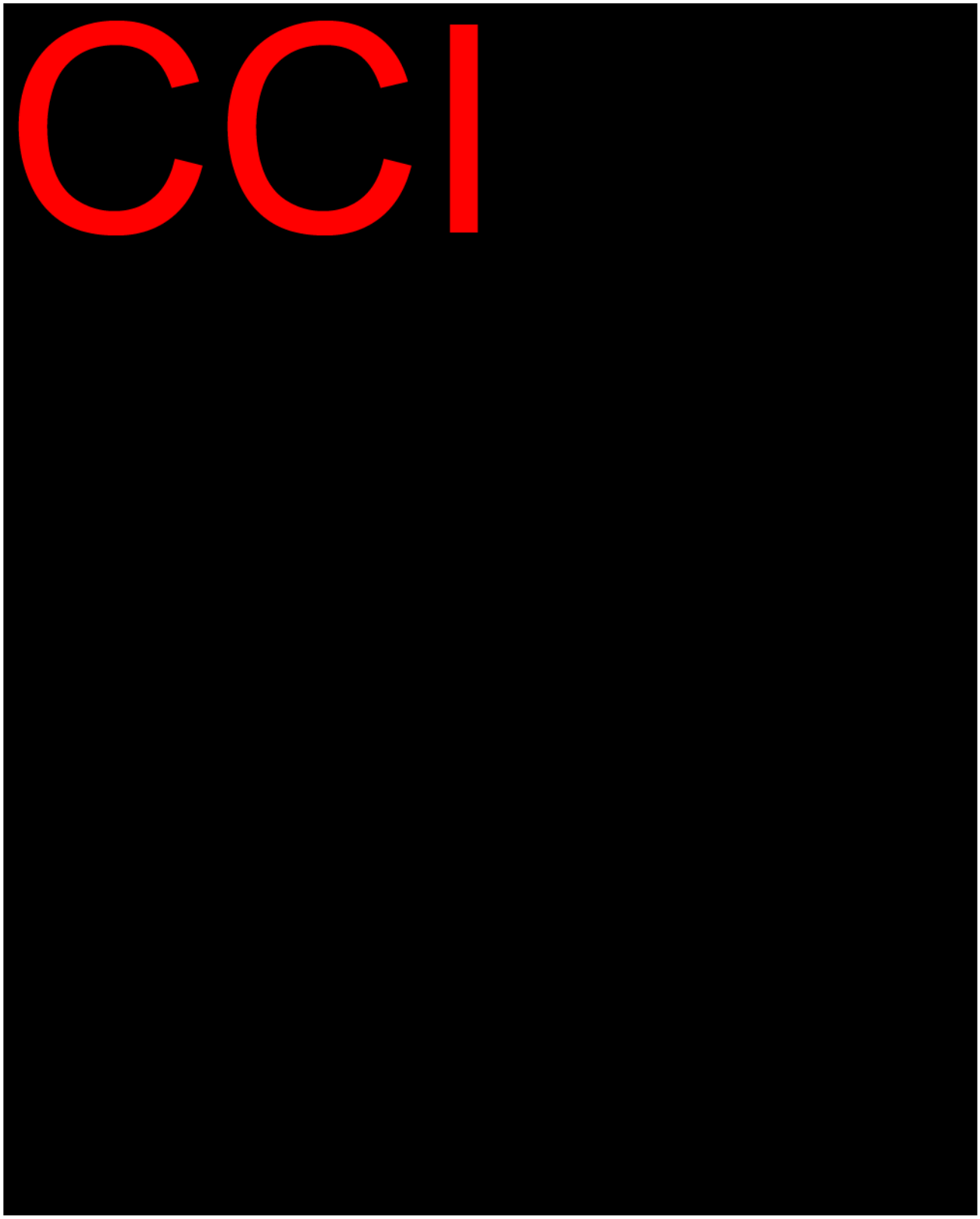
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15.3.4 Anemic Response Rate in patients who are non-TD at enrolment

15.3.4.1 Definition

This is a secondary endpoint for cohorts 1B and 2B as well as for arm 3. Not applicable for cohorts 1A and 2A and for arm 4.

Anemic response rate is defined as a ≥ 1.5 g/dL average increase (after applying the 14/3-day rule, see section 15.3.1.1*) from baseline in any 12-week mean hemoglobin concentration, as calculated over any rolling 12-week (84 days) period post-baseline in the absence of red blood cell (RBC) transfusions and up to the latest Hgb assessment for each patient.

See section 6.1.15 for baseline definition for anemic response. See sections 22.4 and 22.6 for details on analysis visit windows and on unscheduled visits, respectively. See section 21.1 for handling of missing data. See section 15.2.1.1 for the definition of TI.

*Note: for the selection of valid Hgb assessments for the derivation of anemic response, the same specifications as detailed in section 15.3.1.1 will be applied, with the only exception that rolling 12-week (i.e., 84 days) intervals are identified for anemic response.

15.3.4.2 Analysis

Arm/Cohort: cohort 1B, cohort 2B, arm 3.

Main analysis

Data will be presented for each arm and overall. For arms 1 and 2, data will be presented by arm and cohort (i.e., 1B, 2B). Anemic response rate will be analyzed as detailed below.

- The following will be presented:

    a. The number and percentage of patients in the ITT set for cohorts 1B and 2B and arm 3 who are non-TD at enrolment;
    b. The number and percentage of patients in the ITT set for cohorts 1B and 2B and arm 3 who enrolled as TD.

- The number and percentage of patients achieving anemic response throughout the study will be summarized, along with exact 95% confidence limits for the binomial distribution. This will be computed over (a) above. Early discontinued patients before week 12 will be considered as non-responders.
- A summary of Hgb distribution by cycle will be provided (see sections 6.1.4 and 23 for cycle definition and for details on the by-cycle assessments, respectively). Patients with non-missing baseline will be included in this summary even if the post-baseline assessments are not available. The summary will also show the number and percentage of missing data at baseline as well at each post-baseline assessment.
- The distribution of Hgb by cycle for the following subgroups of patients will be included in the summary above as separate tabs:

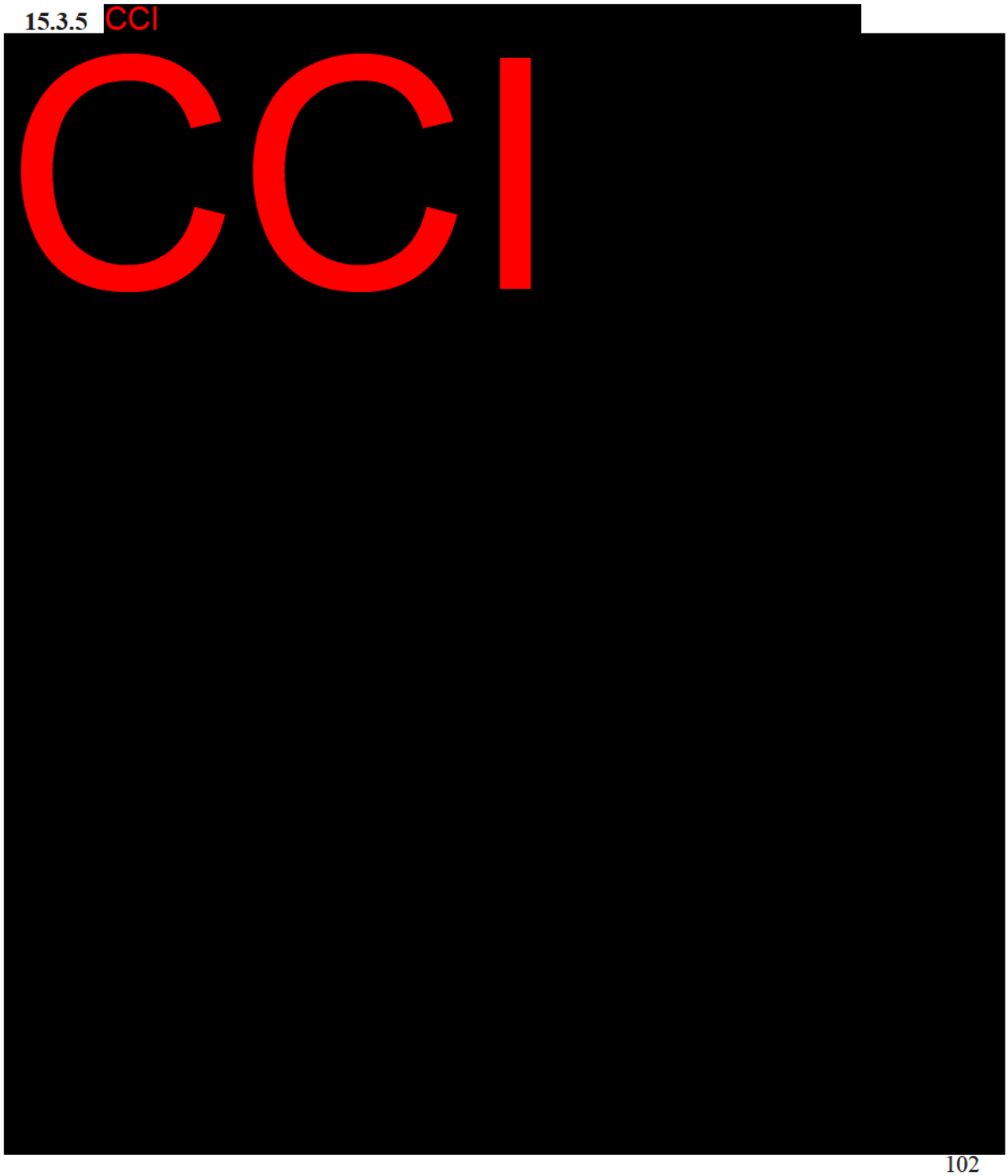
    - Baseline Hgb < 10 g/dL
    - Baseline Hgb ≥ 10 g/dL

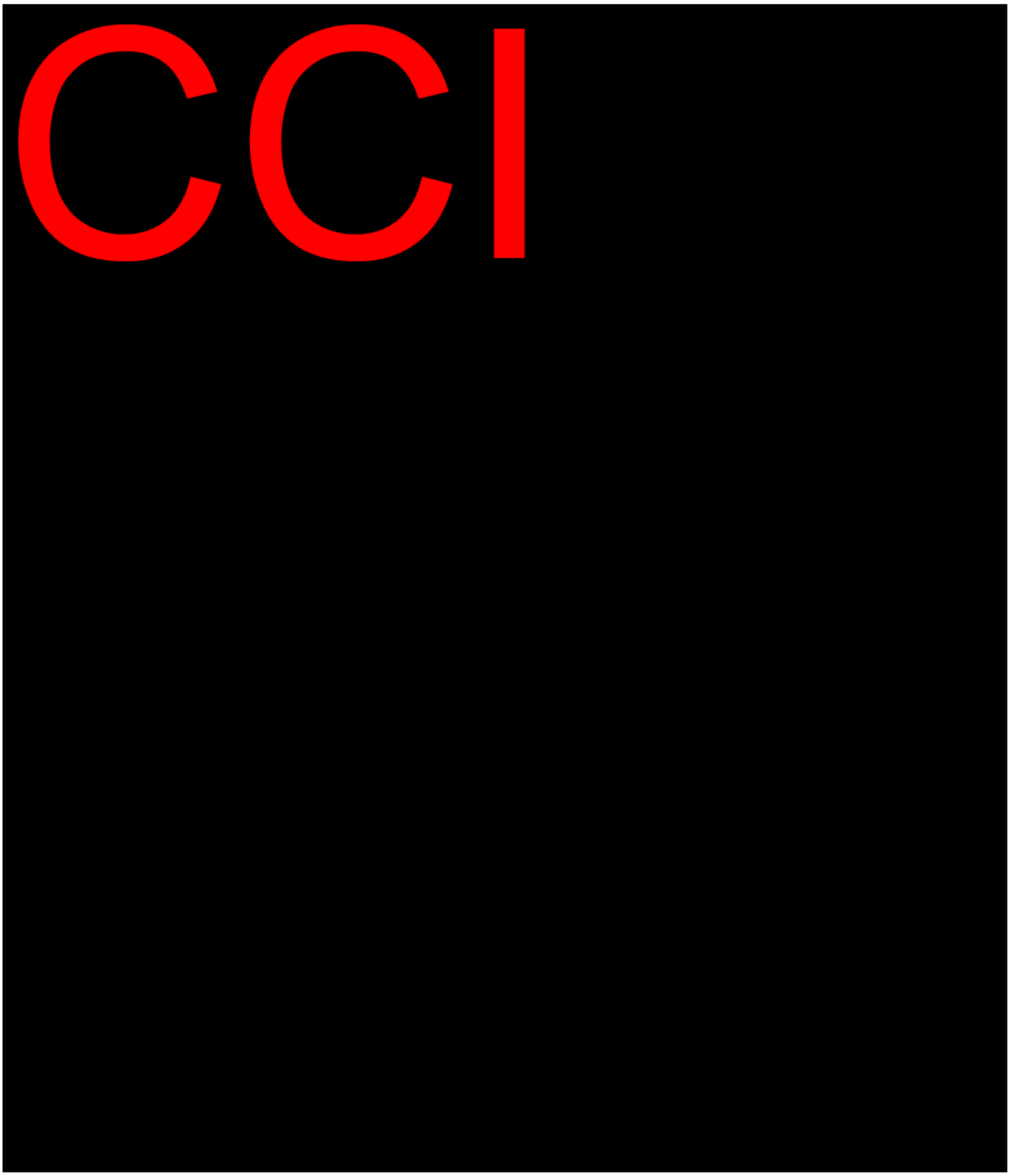
- The distribution of Hgb by cycle and by baseline Hgb subgroups (see above) by cycle will also be presented graphically using boxplots.

Note: Hgb in g/dL will be derived from the Hgb values in SI unit (i.e., g/L). To obtain g/dL, Hgb value in g/L will be divided by 10.

See: section 6.1.15 for the definition of baseline anemic response; sections 22.4 and 22.6 for, respectively, visit windows definition and unscheduled visits; section 21.1 for imputation rules for (early) anemic response.

15.3.5 CCI

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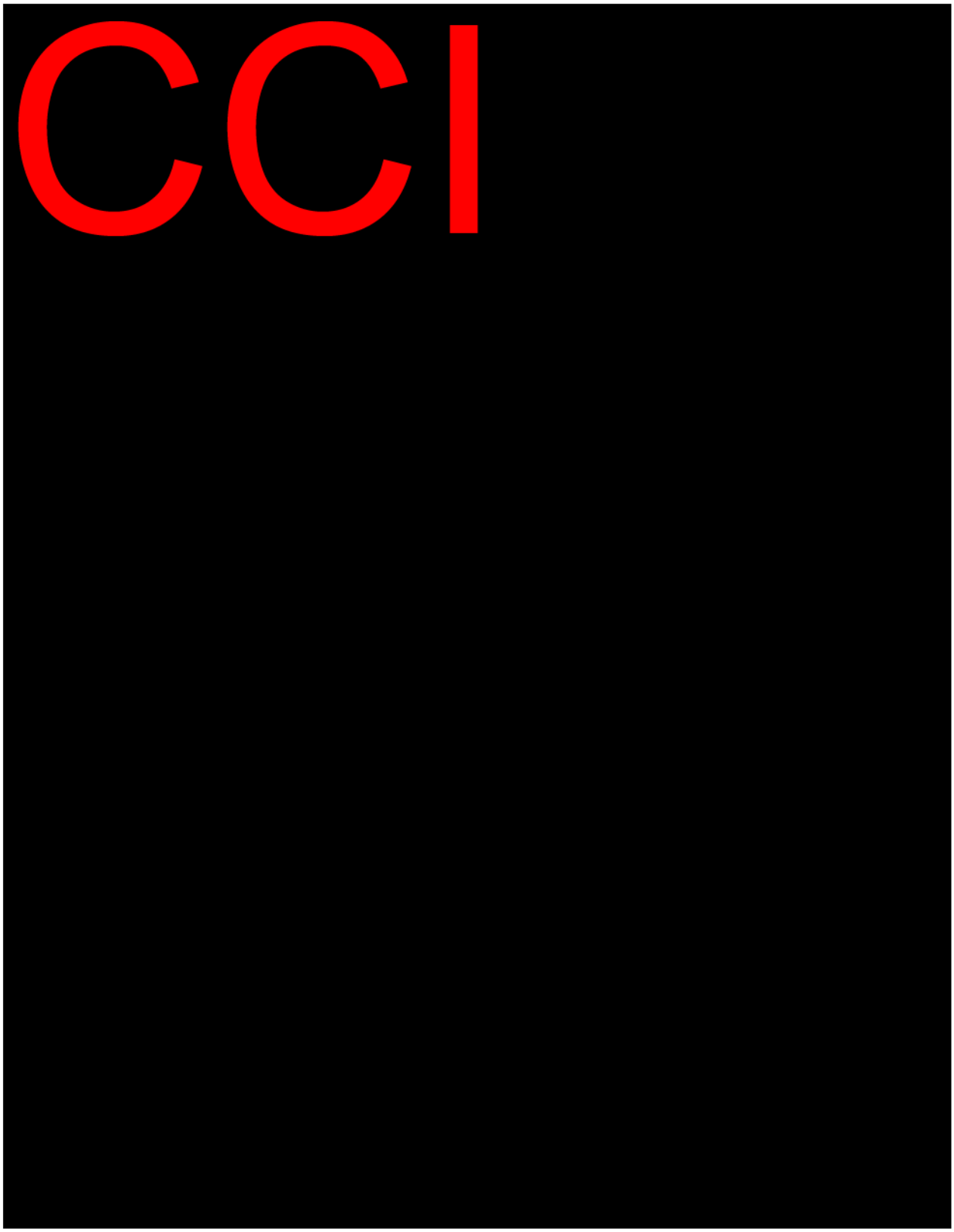
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15.3.7 Complete hematological response rate (CHR)

15.3.7.1 Definition

This is the primary endpoint for arm 4. Not applicable for arms 1 and 2 (all cohorts) and for arm 3.

The complete hematological response rate (CHR) is defined as the proportion of patients who meet the following criteria over two consecutive cycles up to last administration of study treatment:

- Platelet count ≤ 400 x 10^9/L and white blood cell (WBC) count within normal range (i.e., ≤ 10 x 10^9/L);
- Laboratory results above confirmed after 1 cycle - i.e., confirmed over 2 consecutive cycles*;
- Normal spleen size by palpation or imaging (the spleen size by palpation is defined as "normal" when the palpation is entered as "not palpable" in the eCRF page for spleen size)**.

*Confirmed over 2 consecutive cycles do not require exact 21 days between the given laboratory assessment over the 2 cycles. As long as the laboratory assessments are done within each cycle (+/- 5 days of the scheduled day), then the laboratory assessments can be used.

**Spleen size by palpation is assessed at cycles 1, 2, 3 and every odd numbered cycles thereafter (see schedule of events for details). For cycles in which spleen size is not assessed (e.g., cycles 4, 6, etc.), the assessment from the nearest cycle will be used, as long as this falls within the +/-3 weeks window. For example, spleen size by palpation is not collected at cycle 4. In which case, the assessment performed at cycle 3 may be used.

For baseline spleen size refer to section 6.1.13. For baseline for the laboratory parameters (i.e., platelet and WBC), refer to section 6.1.17. For details about treatment cycles, see section 6.1.4.

15.3.7.2 Analysis

Arm/Cohort: arm 4.

Main analysis

CHR will be analysed as detailed below.

- The following will be provided:
    a. The number and percentage of patients in the ITT set for arm 4 with at least 1 follow-up platelet and WBC assessment during the study;
    b. The number and percentage of patients in the ITT set for arm 4 with no follow-up platelet and WBC assessment during the study.

- The number and percentage of patients who achieve a CHR will be summarized; exact 95% confidence limits of the binomial distribution will be provided. This rate will be computed over (a) above. Patients with a CHR will be considered as responders; patients without CHR as well as patients who discontinued without CHR, will be considered as non-responders; patients who meet the criteria for a CHR for 1 cycle and are still ongoing at the cutoff date will be considered

as unconfirmed responders. The number and percentage of unconfirmed CHR responders will also be summarized.

Sensitivity analysis

The same analysis as described above for the main analysis will be conducted on the PPS analysis set as well.

15.3.8 Partial Hematological Response Rate (PHR)

15.3.8.1 Definition

This is a secondary endpoint for arm 4. Not applicable for arms 1, 2 and 3.

The partial hematological response rate is defined as the proportion of patients who meet the following criteria over two consecutive cycles* up to last administration of study treatment:

- Platelet count > 400-600 x 10^9/L;
- WBC count within normal range (i.e., ≤ 10 x 10^9/L).

*Confirmed over 2 consecutive cycles do not require exact 21 days between the given laboratory assessment over the 2 cycles. As long as the laboratory assessments are done within each cycle (+/- 5 days of the scheduled day), then the laboratory assessments can be used.

For baseline for the laboratory parameters (i.e., platelet and WBC), refer to section 6.1.17. For details about treatment cycles, see section 6.1.4.

15.3.8.2 Analysis

Arm/Cohort: arm 4

Main analysis

PHR will be analyzed as detailed below.

- The following will be provided:
    a. The number and percentage of patients in the ITT set for arm 4 with at least 1 follow-up platelet and WBC assessment during the study;
    b. The number and percentage of patients in the ITT set for arm 4 with no follow-up platelet and WBC assessment during the study.

- The number and percentage of patients who achieve a PHR will be summarized; exact 95% confidence limits of the binomial distribution will be provided. This rate will be computed over (a) above. Patients with a PHR will be considered as responders; patients without PHR as well as patients who discontinued without PHR, will be considered as non-responders; patients who meet the criteria for a PHR for 1 cycle and are still ongoing at the cutoff date will be considered as unconfirmed responders. The number and percentage of unconfirmed PHR responders will also be reported.

15.3.9 Overall Hematological Response Rate (OHR)

15.3.9.1 Definition

This is a secondary endpoint for arm 4. Not applicable for arms 1-3.

The confirmed OHR rate is defined as the proportion of patients with either a confirmed complete (section 15.3.7.1) or a partial (section 15.3.8.1) hematological response at any time.

15.3.9.2 Analysis

Arm/Cohort: arm 4

Main analysis

Overall haematological response will be analysed as detailed below.

- The following will be provided:
    a. The number and percentage of patients in the ITT set for arm 4 with at least 1 follow-up platelet and WBC assessment during the study;
    b. The number and percentage of patients in the ITT set for arm 4 with no follow-up platelet and WBC assessment during the study.

- The number and percentage of patients who achieve an overall hematological response will be summarized overall (i.e., at any time) and every two cycles as well; exact 95% confidence limits of the binomial distribution will be provided. The rate will be computed over (a) above. The number and percentage of patients with an unconfirmed OHR will also be presented. An OHR is considered as unconfirmed if, in the absence of any OHR as defined above, the patient has either an unconfirmed CHR or an unconfirmed PHR or both.

15.3.10 Duration of Overall Hematological Response

15.3.10.1 Definition

This is a secondary endpoint for arm 4. Not applicable for arms 1-3.

The duration of the overall hematological response is defined as the time from when the overall hematological response is first met (section 15.3.9.1) until the time at which the overall hematological response is lost - i.e., the criteria for an overall hematological response (i.e., for a CHR or a partial hematological response) are not observed or death occurred, whichever comes first. In weeks, it is computed as follows:

(Date of loss of overall hematological response* - date of first overall hematological response + 1) / 7

*or date of death, see section 8.5.3.2.

15.3.10.2 **Analysis**

Arm/Cohort: arm 4

Main analysis

Duration of overall hematological response will be analyzed as detailed below. Data will be presented in weeks.

- The following will be provided:
  a. The number and percentage of patients in the ITT set for arm 4 with a OHR.

- The number and percentage of patients with event and number of patients with censoring along with reasons for censoring will be summarized.
- The distribution of the duration time will be estimated using the Kaplan-Meier method. K-M estimate (%) and 95% confidence limits for the K-M estimate (calculated with Greenwood's formula) will be provided at every 2 cycles and at EOT. The median time with 95% confidence intervals will be presented (Brookmeyer and Crowley, 1982). The 25th and 75th percentiles will be estimated as well, along with their 95% confidence limits.

The distribution of patients with event/censoring, as well as the K-M statistics, will be computed over (a) above. See sections 8.5.3.1 and 8.5.3.2 for details for the K-M estimates and for the censoring strategy and reasons, respectively.

15.3.11 Composite OHR and MPN-SAF TSS50 response rate

15.3.11.1 **Definition**

This is a secondary endpoint for arm 4. Not applicable for arms 1-3.

The composite OHR and MPN-SAF TSS50 response rate is defined as the proportion of patients who achieve both a OHR (see definition is section 15.3.9.1) and a TSS50 as measured from the MPN-SAF (see definition in section 15.5.4.1) simultaneously (i.e., OHR and MPN-SAF TSS50 responses have to overlap in the same time window in order for this to be considered a composite response).

15.3.11.2 **Analysis**

Arm/Cohort: arm 4.

Main analysis

This composite response will be analyzed as detailed below.

- The following will be provided:
    a. The number and percentage of patients in the ITT set for arm 4 evaluable for the composite OHR and MPN-SAF TSS50 response (see details below);
    b. The number and percentage of patients in the ITT set for arm 4 non-evaluable for the composite OHR and MPN-SAF TSS50 response, along with reasons for non-evaluability (see details below).

- The number and percentage of patients achieving both a OHR and a MPN-SAF TSS50 response will be summarized; exact 95% confidence limits of the binomial distribution will be provided for a more precise estimation of the binomial distribution. The rate will be computed over (a) above. Patients with a composite OHR and MPN-SAF TSS50 will be considered as responders. Patients without composite response will be considered as non-responders.

Patients who meet the evaluability criteria for both OHR and the MPN-SAF TSS50 will be evaluable for the composite response. See section 15.3.9 for patients' evaluability for OHR and section 15.5.6 for patients' evaluability for the MPN-SAF TSS50.

Patients who do not meet the evaluability criteria of one or both the endpoints (i.e., OHR and/or MPN-SAF TSS50) will be non-evaluable for the composite response. The possible reasons for patients' non-evaluability are listed below:

- Non-evaluable for OHR;
- Non-evaluable for MPN-SAF TSS50;
- Non-evaluable for OHR and MPN-SAF TSS50.

15.3.12 Duration of composite OHR and MPN-SAF TSS50 response

15.3.12.1 Definition

This is a secondary endpoint for arm 4. Not applicable for arms 1-3.

The duration of this composite response is defined as the time from the first composite OHR and MPN-SAF TSS50 response is met until the time at which the response is lost or death occurred, whichever comes first. It is computed in weeks as follows:

(Date of loss of composite response* - date of first composite response + 1) / 7

*or date of death, see section 8.5.3.2.

Where:

- Date of first composite response: it is the first date at which the composite OHR and MPN-SAF TSS50 are observed.
- Date of loss of composite response: for patients who had reached a composite response, it is the first date at which either the overall hematological response or the TSS50 from the MPN-SAF is lost (i.e., at least one of them).

15.3.12.2 **Analysis**

Arm/Cohort: arm 4.

Main analysis

Duration of composite OHR and MPN-SAF TSS50 response will be analysed as detailed below. Data will be presented in weeks.

- The following will be provided:
    a. The number and percentage of patients who had a composite OHR and MPN-SAF TSS50 response.

- The number and percentage of patients with event and number of patients with censoring along with reasons for censoring will be summarized.
- The distribution of the duration time will be estimated using the Kaplan-Meier method. . K-M estimate (%) and 95% confidence limits for the K-M estimate (calculated with Greenwood's formula) will be provided at every 12 weeks and at EOT. The median time with 95% confidence intervals will be presented (Brookmeyer and Crowley, 1982). The 25th and 75th percentiles will be estimated as well, along with their 95% confidence limits.

Both the distribution of patients with event/censoring and the K-M statistics will be computed over (a) above. See sections 8.5.3.1 and 8.5.3.2 for details for the K-M estimates and for the censoring strategy, respectively.

15.3.13 Rate of hemorrhagic and thromboembolic (TE) events

15.3.13.1 **Definition**

This is a secondary endpoint for arm 4. Not applicable for arms 1-3.

The rate is defined as the proportion of patients with hemorrhagic or TE events throughout the study.

15.3.13.2 **Analysis**

Arm/Cohort: arm 4.

Main analysis

The following will be provided:

- The number and percentage of patients in the ITT set for arm 4 with a hemorrhagic or a TE event will be summarized over time; exact 95% confidence limits of the binomial distribution will be provided.

Patients with two or more hemorrhagic/TE events will be counted for each event.

15.4 Splenic Volume Reduction

15.4.1 Splenic response rate at week 24 (SVR35 at week 24)

15.4.1.1 Definition

This is the primary endpoint for cohorts 1B and 2B and for arm 3, and secondary endpoint for cohorts 1A and 2A. Not applicable for arm 4.

Splenic response rate at week 24 (SVR35) is defined as a ≥35% reduction from baseline spleen volume as measured by MRI or CT at week 24 (Cycle 9, Day 1) - see section 6.1.13 for baseline definition.

Site reported spleen volume values will be used for the analysis. If the site only reported the parameters of the spleen, then the spleen volume will be calculated in cm^3 as follows:

$$\text{Spleen volume} = 30 + 0.58*(\text{Length} \times \text{Width} \times \text{Thickness})$$

15.4.1.2 Analysis

Arm/Cohort: arms 1, 2 and 3.

Baseline definition for Spleen volume is provided in section 6.1.13. Details on the analysis visit windows and unscheduled visits are provided in sections 22.1 and 22.6, respectively. Details on imputation rules are provided in section 21.1.

Main analysis

Splenic response at week 24 will be analyzed as detailed below.

For Arms 1, 2 (all cohorts) and 3:

- The following will be provided:
    a. The number and percentage of patients in the ITT set evaluable for SVR35 at week 24 (see details below);
    b. The number and percentage of patients in the ITT set non-evaluable for SVR35 at week 24, along with reasons for non-evaluability (see details below).

- The number and percentage of patients achieving a ≥ 35% reduction from baseline in spleen volume at week 24 will be summarized; exact 95% confidence limits of the binomial distribution will be provided. The rate will be computed over (a) above. Patients will be considered as responders/non-responders based on what follows:
    - Patients with a ≥ 35% reduction in spleen volume at week 24: responders
    - Patients without a ≥ 35% reduction in spleen volume at week 24: non-responders
    - Patients with missing week 24 spleen volume per visit window: non-responders
    - Patients with missing week 24 spleen volume and who discontinued (based on the date of end of treatment) before week 19 (Day 127): non-responders.
- The percent change from baseline to week 24 in spleen volume will be summarized and it will also be presented using a waterfall plot. The percent change summary will also display: the number of data not-available at baseline and at week 24; the number and percentage of patients with >0% reduction in spleen volume. The waterfall plot will display one bar for each patient included in the analysis and will be sorted in descending order.

A listing of non-evaluable patients for SVR35 at week 24 with reasons for non-evaluability (see details below) will be generated.

The table below describes the criteria for patients' evaluability/non-evaluability for SVR35 at week 24, as well as the possible reasons for non-evaluability.

Criterion	**(Non-)evaluability**	**Rationale for non-evaluability**	**Reason for non-evaluability**
For on-going patients at data cutoff date/completers			
Have non-zero/non-missing spleen volume at baseline, and have spleen volume on/beyond week 19 (Day 127).	Evaluable		
Only for Cohorts 1A and 2A: Have baseline spleen size on imaging ≥ 450 cm^3.	Evaluable		
Have spleen volume=0 or missing at baseline.	Non-evaluable	(Ongoing at cutoff date with) baseline spleen volume = 0 or missing. Percent change from baseline cannot be computed.	Non-evaluable baseline spleen volume

Only for Cohorts 1A and 2A: Have baseline spleen size on imaging < 450 cm^3.	Non-evaluable	(Ongoing at cutoff date with) baseline spleen volume < 450 cm^3. Baseline spleen volume size does not meet protocol requirement (see protocol section 7.2.4.1).	Non-evaluable baseline spleen volume
Have non-zero/non-missing spleen volume at baseline, but have no spleen volume on/beyond week 19 (Day 127).	Non-evaluable	(Ongoing at cutoff date with) no spleen volume on/beyond week 19. Week 24 SVR may not happen yet or it is not available per visit window and/or imputation.	Not-available spleen volume value at week 24
For discontinued patients			
Have non-missing and non-zero baseline. For cohorts 1A and 2A only: Have baseline spleen size on imaging ≥ 450 cm^3.	Evaluable		
Have spleen volume=0 or missing at baseline but withdraw (based on the date of the end of treatment) before week 19 (Day 127).	Evaluable		
For cohorts 1A and 2A only: Have baseline spleen size on imaging < 450 cm^3 but withdraw (based on the date of the end of treatment) before week 19 (Day 127).	Evaluable		
Have spleen volume=0 or missing at baseline but withdraw (based on the date of the end of treatment) on/after week 19 (Day 127).	Non-evaluable	Have baseline spleen volume = 0/missing and discontinued on/after week 19. Percent change from baseline cannot be computed.	Non-evaluable baseline spleen volume

For cohorts 1A and 2A only: Have baseline spleen volume < 450 cm^3 but withdraw (based on the date of the end of treatment) on/after week 19 (Day 127).	Non-evaluable	Have baseline spleen volume < 450 cm^3 and discontinued on/after week 19. Baseline spleen volume size does not meet protocol requirement (see protocol section 7.2.4.1).	Non-evaluable baseline spleen volume

Sensitivity Analysis

The following four sensitivity analyses will be conducted.

(1) Arm 3 only: SVR35 at weeks 24 and 48 from central imaging records

For patients in arm 3, SVR35 will be analyzed using central imaging records at the following time-points: week 24, week 48.

For each of the time-points above, SVR35 will be analyzed as detailed below.

- The following will be provided:

    a. The number and percentage of patients in the ITT set evaluable for SVR35 at week 24/48;
    b. The number and percentage of patients in the ITT set non-evaluable for SVR35 at week 24/48, along with reasons for non-evaluability.

- The number and percentage of patients achieving a ≥ 35% reduction from baseline in spleen volume at week 24/48 will be summarized; exact 95% confidence limits of the binomial distribution will be provided. The rate will be computed over (a) above. Patients will be considered as responders/non-responders based on what follows:

    - Patients with a ≥ 35% reduction in spleen volume at week 24/48: responders
    - Patients without a ≥ 35% reduction in spleen volume at week 24/48: non-responders
    - Patients with missing week 24/48 spleen volume per visit window: non-responders
    - Patients with missing week 24 spleen volume and who discontinued (based on the date of end of treatment) before week 19 (Day 127): non-responders.
    - Patients with missing week 48 spleen volume and who discontinued (based on the date of end of treatment) before week 43 (Day 295): non-responders.

See main analysis above for patients' evaluability/non-evaluability criteria for week 24; see supportive and additional analysis for (non-)evaluability at week 48.

(2) SVR25 at week 24 (Arms 1 and 2 only)

In arms 1 and 2, the splenic response rate will be analysed by looking at SVR25 at week 24. SVR25 at week 24 is defined as a ≥ 25% reduction from baseline spleen volume as measured by MRI or CT at week 24 (Cycle 9, Day 1).

Site reported spleen volume values will be used for the analysis. If only site-reported spleen parameters are available, apply the formula as provided in section 15.4.1.1.

SVR25 at week 24 will be analysed as described below. Data will be presented by arm and cohort.

- The following will be provided:

  a. The number and percentage of patients in the ITT set evaluable for SVR25 at week 24 (see patients' evaluability/non-evaluability in main analysis for SVR35 at week 24);
  b. The number and percentage of patients in the ITT set non-evaluable for SVR25 at week 24, along with reasons for non-evaluability (see patients' evaluability/non-evaluability in main analysis for SVR35 at week 24).

- The number and percentage of patients achieving a $\geq$ 25% reduction from baseline in spleen volume at week 24 will be summarized; exact 95% confidence limits of the binomial distribution will be provided. The rate will be computed over (a) above. Patients will be considered as responders/non-responders based on what follows:

  - Patients with a $\geq$ 25% reduction in spleen volume at week 24: responders
  - Patients without a $\geq$ 25% reduction in spleen volume at week 24: non-responders
  - Patients with missing week 24 spleen volume per visit window: non-responders
  - Patients with missing week 24 spleen volume and who discontinued (based on the date of end of treatment) before week 19 (Day 127): non-responders.

(3) SVR35 without imputation for missing spleen volume values

The same analyses as detailed for main analysis above on SVR35 will be conducted without applying imputation rule (1) - see section 21.1 - for missing spleen volume value at an analysis visit.

(4) Analysis on the PPS analysis set

The same analyses as described for what listed below will be conducted on the PPS analysis set:

- Main analysis,
- Sensitivity analyses (1), (2) and (3),
- Concordance analysis (see below),
- Supportive and additional analysis (see below),
- Subgroup analyses (1)-to-(3) (see below).

Concordance analysis:

(1) Arm 3 only: Concordance rate between central and local imaging records on SVR35

This analysis on SVR35 imaging data at week 24 is aimed at evaluating the concordance between central and local imaging records for patients in arm 3 - i.e., the concordance between the number of SVR35 responders and non-responders at week 24 in central versus local records. The concordance rate will be computed both including and excluding missing data (see below).

The central and local imaging SVR data records will be 1-to-1 matched. Afterwards, the concordance rate will be computed as indicated in Table 4 below.

Table 4: Computation of the concordance rate between central and local imaging SVR data records

		Local			
Central		Responder	Non-Responder	Missing	Total
	Responder	a	b	c	d
	Non-Responder	e	f	g	h
	Missing	i	j	k	l
	Total	m	n	o	p
		Concordance rate excluding missing data		$100 * \frac{(a+f)}{(a+b+e+f)}$	
		Concordance rate including missing data		$100 * \frac{(a+f+k)}{p}$	

(2) Concordance rate between SVR35 and MFSAF TSS50 responders/non-responders at week 24

This concordance analysis is aimed at analysing the concordance between the number of responders and non-responders at week 24 in SVR35 versus the MFSAF TSS50. The concordance rate will be computed both including and excluding missing data.

The data on SVR35 and MFSAF TSS50 will be 1-to-1 matched. Afterwards, the concordance rate will be computed as indicated in Table 5 below.

Table 5: Computation of the concordance rate between SVR35 and TSS50 responders/non-responders at week 24

		SVR35 at week 24			
MFSAF TSS50 at week 24		Responder	Non-Responder	Missing	Total
	Responder	a	b	c	d
	Non-Responder	e	f	g	h
	Missing	i	j	k	l
	Total	m	n	o	p
		Concordance rate excluding missing data		$100 * \frac{(a+f)}{(a+b+e+f)}$	
		Concordance rate including missing data		$100 * \frac{(a+f+k)}{p}$	

Supportive and additional analysis

A set of additional analyses will be conducted on SVR35 by considering additional post-baseline assessments, namely SVR35 at week 36, week 48, week 60, week 72 and every 12 weeks thereafter. These are defined below.

1. SVR35 at week 36

This is defined as a ≥ 35% reduction from baseline spleen volume as measured by MRI or CT at week 36.

2. SVR35 at week 48

This is defined as a ≥ 35% reduction from baseline spleen volume as measured by MRI or CT at week 48.

3. SVR35 at week 60

This is defined as a ≥ 35% reduction from baseline spleen volume as measured by MRI or CT at week 60.

4. SVR35 at week 72 and every 12 weeks thereafter

SVR35 at week 72 is defined as a ≥ 35% reduction from baseline spleen volume as measured by MRI or CT at week 72.

SVR35 at every 12 weeks after week 72 is defined as a ≥ 35% reduction from baseline spleen volume as measured by MRI or CT at the given week (i.e., week 84, week 96, week 108, etc.).

For all of the above, site reported spleen volume values will be used for the analysis. If the site only reported the parameters of the spleen, then the spleen volume will be calculated using the formula provided in section 15.4.1.1

SVR35 at week 36, 48, 60, 72 and every 12 weeks thereafter will be analysed as detailed for arms 1, 2 and 3 in the main analysis on SVR35 at week 24. Data will be presented by arm and cohort (where relevant), as well as overall.

The criteria for patients' evaluability/non-evaluability for these analyses, together with possible reasons for non-evaluability, are specified in Table 6.

For the computation of the number and percentage of patients with SVR35 at week 36/48/60/72 and every 12 weeks thereafter, patients will be classified as responders/non-responders based on what described below.

For SVR35 at weeks 36/48/60/72:

- Patients with a ≥ 35% reduction in spleen volume at the given week (i.e., 36/48/60/72 etc.): responders.

- Patients without a ≥ 35% reduction in spleen volume at the given week: non-responders.
- Patients with missing spleen volume at the given week per visit window: non-responders.
- Patients with missing week 36 spleen volume and who discontinued (based on the date of end of treatment) before week 31 (Day 211): non-responders.
- Patients with missing week 48 spleen volume and who discontinued (based on the date of end of treatment) before week 43 (Day 295): non-responders.
- Patients with missing week 60 spleen volume and who discontinued (based on the date of end of treatment) before week 55 (Day 379): non-responders.
- Patients with missing week 72 spleen volume and who discontinued (based on the date of end of treatment) before week 67 (Day 463): non-responders.

For SVR35 at every 12 weeks after week 72:

- Patients with missing spleen volume at the given week and who discontinued (based on the date of end of treatment) before the lower bound of the analysis visit window of the week under scrutiny (see Table 17 in section 22.1): non-responders. For example, patients with missing week 84 spleen volume and who discontinued (based on the date of end of treatment) before Day 547 (week 79) will be considered as non-responders.

Additionally, for SVR35 at week 48 (i.e., (2) above), concordance analysis (1) as described above will be conducted.

Table 6: Patients' evaluability for SVR35 at week 36, 48, 60, 72 and every 12 weeks thereafter

Criterion	(Non-)evaluability	Rationale for non-evaluability	Reason for non-evaluability
For patients on treatment at corresponding timepoint of analysis			
Have non-zero/non-missing spleen volume at baseline, and have spleen volume on/beyond: - For SVR35 at week 36: week 31 (Day 211). - For SVR35 at week 48: week 43 (Day 295). - For SVR35 at week 60: week 55 (Day 379). - For SVR35 at week 72: week 67 (Day 463). - For SVR35 at every 12 weeks after week 72: the lower bound of the analysis visit window of the week under scrutiny (see Table 17 in section 22.1). For example, for SVR35 at week 84, this	Evaluable		

would be Day 547 (week 79).			
Only for Cohorts 1A and 2A: Have baseline spleen size on imaging $\geqslant$ 450 cm^3.	Evaluable		
Have spleen volume=0 or missing at baseline.	Non-evaluable	(Ongoing at cutoff date with) baseline spleen volume = 0 or missing. Percent change from baseline cannot be computed.	Non-evaluable baseline spleen volume
Only for Cohorts 1A and 2A: Have baseline spleen size on imaging < 450 cm^3.	Non-evaluable	(Ongoing at cutoff date with) baseline spleen volume < 450 cm^3. Baseline spleen volume size does not meet protocol requirement (see protocol section 7.2.4.1).	Non-evaluable baseline spleen volume
Have non-zero/non-missing spleen volume at baseline, but have no spleen volume on/beyond: - For SVR35 at week 36: week 31 (Day 211). - For SVR35 at week 48: week 43 (Day 295). - For SVR35 at week 60: week 55 (Day 379). - For SVR35 at week 72: week 67 (Day 463). - For SVR35 at every 12 weeks after week 72: the lower bound of the analysis visit window of the week under scrutiny (see Table 17 in section 22.1). For example, for SVR35 at week 84, this would be Day 547 (week 79).	Non-evaluable	(Ongoing at cutoff date with) no spleen volume on/beyond: - Week 31 (for SVR35 at week 36). - Week 43 (for SVR35 at week 48). - Week 55 (for SVR35 at week 60). - Week 67 (for SVR35 at week 72). - Week n* (for SVR35 at every 12 weeks after week 72). *where week n is the week under which the lower bound of the analysis visit window of the week under scrutiny falls (e.g., week 79 for SVR35 at week 84). SVR for the week under scrutiny may not happen yet or it is not available	Not-available spleen volume value at week 36/48/60/72/n+12*. *<u>*Note*</u>: depending on the week under scrutiny.

		per visit window and/or imputation.	
For discontinued patients			
Have non-zero/non-missing baseline spleen volume. For cohorts 1A and 2A only: Have baseline spleen size on imaging $\geqslant$ 450 cm^3.	Evaluable		
Have spleen volume=0 or missing at baseline but withdraw (based on the date of the end of treatment) before: - For SVR35 at week 36: week 31 (Day 211). - For SVR35 at week 48: week 43 (Day 295). - For SVR35 at week 60: week 55 (Day 379). - For SVR35 at week 72: week 67 (Day 463). - For SVR35 at every 12 weeks after week 72: the lower bound of the analysis visit window of the week under scrutiny (see Table 17 in section 22.1). For example, for SVR35 at week 84, this would be Day 547 (week 79).	Evaluable		
For cohorts 1A and 2A only: Have baseline spleen size on imaging < 450 cm^3 but withdraw (based on the date of the end of treatment) before: - For SVR35 at week 36: week 31 (Day 211).	Evaluable		

- For SVR35 at week 48: week 43 (Day 295). - For SVR35 at week 60: week 55 (Day 379). - For SVR35 at week 72: week 67 (Day 463). - For SVR35 at every 12 weeks after week 72: the lower bound of the analysis visit window of the week under scrutiny (see Table 17 in section 22.1). For example, for SVR35 at week 84, this would be Day 547 (week 79).			
Have spleen volume=0 or missing at baseline but withdraw (based on the date of the end of treatment) on/after: - For SVR35 at week 36: week 31 (Day 211). - For SVR35 at week 48: week 43 (Day 295). - For SVR35 at week 60: week 55 (Day 379). - For SVR35 at week 72: week 67 (Day 463). - For SVR35 at every 12 weeks after week 72: the lower bound of the analysis visit window of the week under scrutiny (see Table 17 in section 22.1). For example, for SVR35 at week 84, this would be Day 547 (week 79).	Non-evaluable	Have baseline spleen volume = 0/missing and discontinued on/after: - Week 31 (for SVR35 at week 36). - Week 43 (for SVR35 at week 48). - Week 55 (for SVR35 at week 60). - Week 67 (for SVR35 at week 72). - Week n* (for SVR35 at every 12 weeks after week 72). *where week n is the week under which the lower bound of the analysis visit window of the week under scrutiny falls (e.g., week 79 for SVR35 at week 84). Percent change from baseline cannot be computed.	Non-evaluable baseline spleen volume
For cohorts 1A and 2A only: Have baseline spleen volume < 450 cm^3 but	Non-evaluable	Have baseline spleen volume < 450 cm^3 and discontinued on/after:	Non-evaluable baseline spleen volume

withdraw (based on the date of the end of treatment) on/after: - For SVR35 at week 36: week 31 (Day 211). - For SVR35 at week 48: week 43 (Day 295). - For SVR35 at week 60: week 55 (Day 379). - For SVR35 at week 72: week 67 (Day 463). - For SVR35 at every 12 weeks after week 72: the lower bound of the analysis visit window of the week under scrutiny (see Table 17 in section 22.1). For example, for SVR35 at week 84, this would be Day 547 (week 79).		- Week 31 (for SVR35 at week 36). - Week 43 (for SVR35 at week 48). - Week 55 (for SVR35 at week 60). - Week 67 (for SVR35 at week 72). - Week n* (for SVR35 at every 12 weeks after week 72). *where week n is the week under which the lower bound of the analysis visit window of the week under scrutiny falls (e.g., week 79 for SVR35 at week 84). Baseline spleen volume size does not meet protocol requirement (see protocol section 7.2.4.1).	

Subgroup Analysis

The set of subgroup analyses as detailed below will be conducted.

(1) The percent reduction in spleen volume from baseline to week 24 will be graphically reported for the subgroup categories as specified in Table 7 below using a forest plot. For each subgroup category, as well as for the overall ITT set (see section 15.4.1.2 for patients' evaluability), the forest plot will display the mean percent reduction in spleen volume from baseline to week 24 as well as the corresponding 95% exact confidence interval.

(2) The splenic response rate at week 24 (SVR35 at week 24) will be graphically displayed for the subgroup categories as specified in Table 7 using a forest plot. For each subgroup category, as well as for the overall ITT set (see section 15.4.1.2 for patients' evaluability), the forest plot will show the splenic response rate at week 24 together with the corresponding 95% exact confidence interval.

Baseline definition for Spleen volume is provided in section 6.1.13. Details on the analysis visit windows and unscheduled visits are provided in sections 22.1 and 22.6, respectively. Details on imputation rules are provided in section 21.1

Table 7: Subgroup categories for subgroup analyses (1), (2) and (5)

Subgroup
Gender (Female, Male)
Age* (> 65 years, ≤ 65 years)
Race
Ethnicity
Region (North America, Europe) - see specifications below.
DIPSS (intermediate-1 risk, intermediate-2 or High risk)
IPSS (intermediate-1 risk, intermediate-2 or High risk)
MF Subtype (PMF, PPV-MF or PET-MF)
Baseline Spleen Volume (> 1800 cc, ≤ 1800 cc)
Baseline Platelet Count (> 200, ≤ 200)
HMR Status (HMR positive, HMR negative)*
ASXL 1 (ASXL 1 positive, ASXL 1 negative)*
JAK2V617F Status (JAK2V617F positive, JAK2V617F negative)*
Prior Hydroxyurea (HU) Therapy (Yes, No)
Time since diagnosis (months) (< Median, ≥ Median)
Time of prior JaKi treatment (months) (< Median, >= Median)*

*<u>*Notes to Table 7:*</u>

- Time of prior Jaki treatment is applicable only for arms 1, and 2. See section 11 for the derivation. For each applicable arm, the median value will be computed and this will be used as the subgroup threshold.

- Further analysis specifications for blood mutation profiling data (i.e., HMR Status, ASXL 1, JAK2V617F Status) are provided in Section 25.

The following will be applied to map Countries into the 3 categories for Region as reported in Table 7 above:

Country	Region
- United States of America (USA) - Canada (CAN)	North America
- Belgium (BEL) - Germany (DEU) - France (FRA) - Great Britain (GBR) - Italy (ITA) - Netherlands (NLD)	Europe

- Poland (POL)	

(3) Arm 1: SVR35 at week 24 by Prior Response to JAK inhibitor (JAKi)

For arm 1 only, SVR35 at week 24 will be analyzed by the following subgroups of prior response to JAKi: Ineligible, Intolerant, Refractory/resistant.

The definition of prior response to JAKi subgroup will be based on the discontinuation reason for prior therapy (see specifications below) with PT = "RUXOLITINIB PHOSPHATE" or "RUXOLITINIB" or "FEDRATINIB" or "PACRITINIB" or "MOMELOTINIB", or "IATACINIB", or with the following reported name: "NS PHARMA JAK2 INHIBITOR" or "NS-018".

If the patient has no JAKi reported, the patient will be classified as "Ineligible".

If patients have multiple records for prior JAKi and had suboptimal response or progression to at least one of them, it will be considered resistant/refractory.

If patients have multiple records for prior JAKi and had no suboptimal response or progression to any of them, the record with the latest start date will be considered. If the day part is missing, the comparison will be done based on the month and year. If both the day and month parts are missing, the comparison will be done based on year.

Discontinuation Reason for (last) prior JAKi	**Subgroup**
Adverse Event	Intolerant
Sub-Optimal Response	Refractory/resistant
Progression	Refractory/resistant
Other, specify	See the next table

If the reported discontinuation reason is "Other, specify", the subgroup will be defined according to what follows:

Text for "Other reason of discontinuation, specify"	**Subgroup**
Due to both adverse event (anemia) and progression	Refractory/resistant
RUXOLITINIB INTOLERANCE	Intolerant
Anemia	Intolerant
worsening counts	Intolerant
switching to INREBIC (fedratinib)-Alternative therapy (dose chg of rux possibly due to intolerance)	Intolerant
stopped on own	Intolerant
loss of response and spleen size progression	Refractory/resistant
ineffective	Refractory/resistant
no response	Refractory/resistant
Refractory to ruxolitinib	Refractory/resistant

Stable disease	Refractory/resistant
resistance to treatment	Refractory/resistant
To go on trial - partial response to all below	Refractory/resistant
no drug response	Refractory/resistant
resistant	Refractory/resistant
Patient discontinued to take part in CPI0160 trial.	Refractory/resistant
Discontinued due to progressive thrombocytosis	Refractory/resistant
Unknown	Intolerant
not answered	Intolerant
Without improvement in fatigue level and worsening anemia	Intolerant
To being considered for Manifest Trial	Intolerant
No Data	Intolerant
Cytopenia	Intolerant
patient stopped on her own due to feet/leg swelling, insomnia, restlessness	Intolerant
Removed from study due to being prescribed lovenox injections.	Intolerant
not response	Refractory/resistant
Intolerance	Intolerant
ineffectiveness	Refractory/resistant
intolerance and resistence	Refractory/resistant
increase on spleen	Refractory/resistant

If the text for "Other reason of discontinuation, specify" is blank, the patient will be assigned to the "Relapsed/Refractory" subgroup.

The same analysis as specified for main analysis of SVR35 at week 24 (for arms 1, 2 and 3 - bullet points 1, 3 and 4) will be performed for subgroup analysis in (3). Data will be presented by cohort and overall. In addition, a listing will be produced on patient s' assignment to each of the prior response to JAKi subgroups - i.e., the listing will indicate which patient in arm 1 is in which subgroup.

(4) Arm 1 and Arm 2: SVR35 at week 24 by line of Prior JAKi Therapy:

For arms 1 and 2 only, SVR35 at week 24 will be analyzed by the following subgroups of patients based on the line of prior JAKi therapy received:

- Patients who received only 1 line of prior JAKi therapy;
- Patients who received > 1 line of prior JAKi therapy.

Where:

- **1 line of prior JAKi therapy** is defined as having received only 1 of the JAKi therapies as specified in subgroup analysis (3) above (e.g., a patient received only Fedratinib);
- **> 1 line of prior JAKi therapy** is defined as having received more than one JAKi therapies as specified in subgroup analysis (3) (e.g., a patient received Fedratinib, afterwards they received Momelotinib).

The same analysis as specified for main analysis of SVR35 at week 24 will be conducted for subgroup analysis (4).

(5) SVR35 at every 12 weeks by subgroups:

The splenic response rate (SVR35) will be summarized by the subgroup categories as specified in Table 7 above, for Arms 1, 2 and 3 at the following timepoints:

- Week 12 (see section 15.4.2);
- Week 24 (see section 15.4.1.1);
- The additional timepoints as defined in (1)-to-(4) in *Supportive and Additional Analysis* above (i.e., weeks 36, 48, 60, 72 and every 12 weeks thereafter).

For each timepoint and subgroup, the following will be provided:

a. The number and percentage of patients in the ITT set evaluable for SVR35 at the given week;
b. The number and percentage of patients achieving ≥ 35% reduction from baseline in spleen volume at the given week will be summarized; exact 95% confidence limits of the binomial distribution will be provided. The rate will be computed over (a) above.

For patients' (non-)evaluability for SVR35 at the given week and for patients' classification as responders/non-responders, see the corresponding specifications provided for each of the week under scrutiny (section 15.4.2.2 for SVR35 at week 12; section 15.4.1.2 for SVR35 at week 24; *Supportive and Additional Analysis* above for SVR35 at later timepoints - i.e., weeks 36/48/60/72 and every 12 weeks thereafter).

Data will be summarized by arm/cohort and overall.

15.4.2 Splenic response rate at week 12 (SVR35 at week 12)

15.4.2.1 Definition

This is a secondary endpoint for arms 1 and 2 (i.e., for both cohorts in each arm) and for arm 3. Not applicable for arm 4.

Splenic response rate at week 12 is defined as a ≥ 35% reduction from baseline spleen volume as measured by MRI or CT at week 12 (Cycle 5, Day 1) - see section 6.1.13 for baseline definition.

Site reported spleen volume values will be used for the analysis. If only site-reported spleen parameters are available, apply the formula as provided in section 15.4.1.1

15.4.2.2 Analysis

Arm/Cohort: arms 1, 2 and 3.

Baseline definition for Spleen volume is provided in section 6.1.13. Details on the analysis visit windows and unscheduled visits are provided in sections 22.1 and 22.6, respectively. Details on imputation rules are provided in section 21.1

Main analysis

For SVR35 at week 12, the same analysis as described for the main analysis of SVR35 at week 24 (i.e., bullet list for arms 1, 2 and 3 - section 15.4.1.2) will be conducted.

For the number and percentage of patients achieving SVR35 at week 12, patients will be considered as responders/non-responders based on what follows:

- Patients with a ≥ 35% reduction in spleen volume at week 12: responders.
- Patients without a ≥ 35% reduction in spleen volume at week 12: non-responders.
- Patients with missing week 12 spleen volume per visit window: non-responders.
- Patients with missing week 12 spleen volume and who discontinued (based on the date of end of treatment) before week 7 (Day 43): non-responders.

The table below describes the criteria for patients' evaluability/non-evaluability for SVR35 at week 12, as well as the possible reasons for non-evaluability.

Criterion	**(Non-)evaluability**	**Rationale for non-evaluability**	**Reason for non-evaluability**
For patients on treatment at corresponding timepoint of analysis			
Have non-zero/non-missing spleen volume at baseline, and have spleen volume on/beyond week 7 (Day 43).	Evaluable		
Only for Cohorts 1A and 2A: Have baseline spleen size on imaging ≥ 450 cm^3.	Evaluable		
Have spleen volume=0 or missing at baseline.	Non-evaluable	(Ongoing at cutoff date with) baseline spleen volume = 0 or missing. Percent change from baseline cannot be computed.	Non-evaluable baseline spleen volume
Only for Cohorts 1A and 2A: Have baseline spleen size on imaging < 450 cm^3.	Non-evaluable	(Ongoing at cutoff date with) baseline spleen volume < 450 cm^3. Baseline spleen volume size does not meet protocol requirement (see protocol section 7.2.4.1).	Non-evaluable baseline spleen volume

Have non-zero/non-missing spleen volume at baseline, but have no spleen volume on/beyond week 7 (Day 43).	Non-evaluable	(Ongoing at cutoff date with) no spleen volume on/beyond week 7. Week 12 SVR may not happen yet or it is not available per visit window and/or imputation.	Not-available spleen volume value at week 12.
For discontinued patients			
Have non-missing and non-zero baseline spleen volume. For cohorts 1A and 2A only: Have baseline spleen size on imaging $\geq$ 450 cm^3.	Evaluable		
Have spleen volume=0 or missing at baseline but withdraw (based on the date of the end of treatment) before week 7 (Day 43).	Evaluable		
For cohorts 1A and 2A only: Have baseline spleen size on imaging < 450 cm^3 but withdraw (based on the date of the end of treatment) before week 7 (Day 43).	Evaluable		
Have spleen volume=0 or missing at baseline but withdraw (based on the date of the end of treatment) on/after week 7 (Day 43).	Non-evaluable	Have baseline spleen volume = 0/missing and discontinued on/after week 7. Percent change from baseline cannot be computed.	Non-evaluable baseline spleen volume
For cohorts 1A and 2A only: Have baseline spleen volume < 450 cm^3 but withdraw (based on the date of the end of treatment) on/after week 7 (Day 43).	Non-evaluable	Have baseline spleen volume < 450 cm^3 and discontinued on/after week 7. Baseline spleen volume size does not meet protocol requirement (see protocol section 7.2.4.1).	Non-evaluable baseline spleen volume

15.4.3 Overall Splenic Response Rate (Overall SVR35)

15.4.3.1 Definition

This is a secondary endpoint for arms 1 and 2 (all cohorts), as well as for arm 3. Not applicable for arm 4.

The overall splenic response is defined as a $\geq$ 35% reduction from baseline spleen volume as measured by MRI or CT at any time between C1D1 (section 6.1.6) and EOS (section 6.1.8) or cutoff whichever is earlier - see section 6.1.13 for baseline definition. See section 21.2 for patients with EOS date < date of last contact.

Site reported spleen volume values will be used for the analysis. If only site-reported spleen parameters are available, apply the formula as provided in section 15.4.1.1.

15.4.3.2 Analysis

Arm/Cohort: arm 1, arm 2, arm 3.

Baseline definition for Spleen volume is provided in section 6.1.13. Details on the analysis visit windows and unscheduled visits are provided in sections 22.1 and 22.6, respectively. Details on imputation rules are provided in section 21.1.

Main analysis

Overall SVR35 will be analyzed as detailed below.

- The following will be provided:

    a. The number and percentage of patients in the ITT set for arms 1, 2 and 3 evaluable for Overall SVR35 (see details below);
    b. The number and percentage of patients in the ITT set for arms 1, 2 and 3 non-evaluable for Overall SVR35, along with reasons for non-evaluability (see details below).

- The number and percentage of patients achieving a $\geq$ 35% reduction from baseline in spleen volume at any time will be summarized; exact 95% confidence limits for the binomial distribution will be provided. This rate will be computed over (a) above. Patients with a $\geq$ 35% reduction from baseline at any time in spleen volume will be considered as responders. Patients without a $\geq$ 35% reduction from baseline at any time in spleen volume, including patients with no post-baseline spleen volume value for any reason will be considered as non-responders.

- The percent change from baseline to each assessment in spleen volume will be summarized. This will be computed only on patients with both a baseline and a post-baseline assessment in spleen volume. The summary will also display the following: the number of data not-available at baseline and at each assessment; the number and percentage of patients with > 0% reduction in spleen volume at each post-baseline assessment. The percent change from baseline to each assessment in spleen volume will also be displayed graphically using a boxplot.

- A waterfall plot for each assessment will be provided. The waterfall plot will display one bar for each patient included in the analysis and will be sorted in descending order. A horizontal dotted line at -35% will be included.

- A listing will be produced showing absolute values and changes from baseline to each post-baseline assessment in spleen volume.

Patients' evaluability/non-evaluability for Overall SVR35:

Criterion	**(Non-)evaluability**	**Rationale for non-evaluability**	**Reason for non-evaluability**
Have non-zero/non-missing spleen volume at baseline.	Evaluable		
Have baseline spleen volume = 0 or missing.	Non-evaluable	Baseline spleen volume = 0 or missing. Percent change from baseline cannot be computed.	Non-evaluable baseline spleen volume
For cohorts 1A and 2A only: Have baseline spleen volume $\geqslant$ 450 cm^3.	Evaluable		
For cohorts 1A and 2A only: Have baseline spleen volume < 450 cm^3.	Non-evaluable	Baseline spleen volume < 450 cm^3. Baseline spleen volume size does not meet protocol requirement (see protocol section 7.2.4.1).	Non-evaluable baseline spleen volume

Supportive and additional analysis

The following additional analysis will be performed:

(1) Overall SVR35 from central imaging records

Overall SVR35 as defined in section 15.4.3.1 will be analysed using central imaging records.

- The following will be provided:
  a. The number and percentage of patients in the ITT set for arms 1, 2 and 3 evaluable for Overall SVR35 (see details above);
  b. The number and percentage of patients in the ITT set for arms 1, 2 and 3 non-evaluable for Overall SVR35, along with reasons for non-evaluability (see details above).

- The number and percentage of patients achieving a $\geq$ 35% reduction from baseline in spleen volume from central reads at any time will be summarized; exact 95% confidence limits for the binomial distribution will be provided. This rate will be computed over (a) above. Patients with a $\geq$ 35% reduction from baseline at any time in spleen volume will be considered as responders.

Patients without a ≥ 35% reduction from baseline at any time in spleen volume, including patients with no post-baseline spleen volume value for any reason will be considered as non-responders.

Subgroup Analysis:

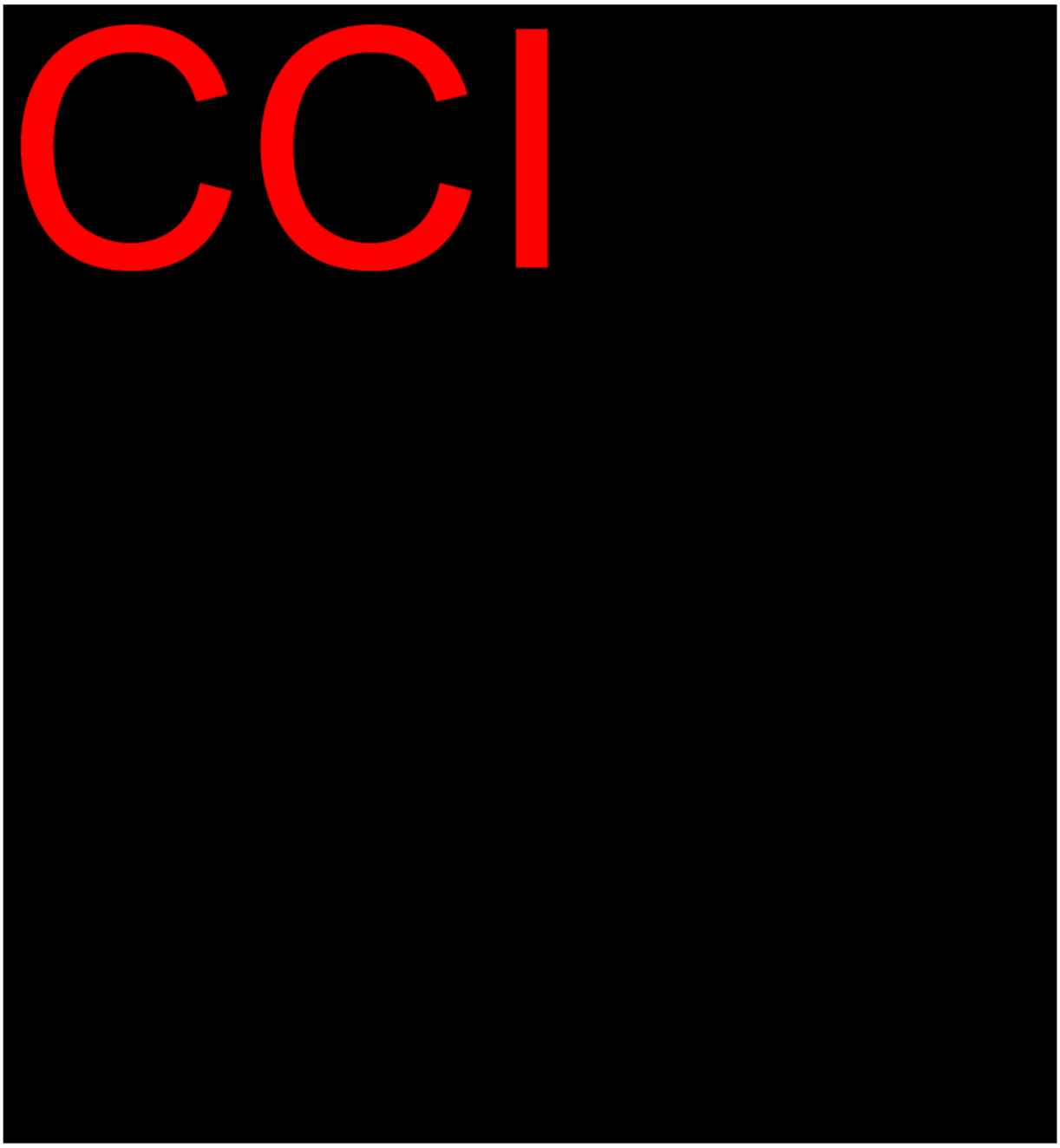
1) Overall SVR35, as defined in section 15.4.3.1, will be summarized by the subgroup categories as specified in Table 7 - section 15.4.1.2.

For each subgroup:

- The following will be provided:
    a. The number and percentage of patients in the ITT set for arms 1, 2 and 3 evaluable for Overall SVR35 (see details as described for *Main Analysis* above);
    b. The number and percentage of patients in the ITT set for arms 1, 2 and 3 non-evaluable for Overall SVR35, along with reasons for non-evaluability (see details as described for *Main Analysis* above).

- The number and percentage of patients achieving a ≥ 35% reduction from baseline in spleen volume at any time will be summarized; exact 95% confidence limits for the binomial distribution will be provided. This rate will be computed over (a) above. Patients with a ≥ 35% reduction from baseline at any time in spleen volume will be considered as responders. Patients without a ≥ 35% reduction from baseline at any time in spleen volume, including patients with no post-baseline spleen volume value for any reason, will be considered as non-responders.

15.4.4 CCI



15.4.5 Duration of the Overall Splenic Response

15.4.5.1 Definition

This is a secondary endpoint for arms 1 and 2 (all cohorts) as well as for arm 3. Not applicable for arm 4.

Duration of the overall splenic response is defined as the time from when the criterion for splenic response is first met (i.e., a ≥ 35% reduction from baseline spleen volume; see section 6.1.13 for baseline definition) until the time at which a < 35% reduction in spleen volume from baseline and also a > 25% increase from the nadir in spleen volume as measured by MRI or CT is first documented, or death, whichever comes first. The nadir is intended to be the lowest post-baseline spleen volume value observed when the first splenic response has been met and up to the evaluation time-point under scrutiny.

Site reported spleen volume values will be used for the analysis. If only site-reported spleen parameters are available, apply the formula as provided in section 15.4.1.1.

Duration of the splenic response is computed in weeks as specified in Table 8 below, where:

- *Date of first splenic response:* it is the first date at which a ≥ 35% reduction from baseline spleen volume as measured by MRI or CT is observed.
- *Date of loss of splenic response:* for patients who had reached a ≥ 35% reduction from baseline spleen volume, it is the first date at which the following is observed: spleen volume as measured by MRI or CT is no longer reduced by at least 35% from baseline and it is increased by > 25% from the nadir in spleen volume.
- *Date of last adequate splenic assessment:* for patients who had reached a ≥ 35% reduction from baseline spleen volume, it is the date of the last MRI or CT splenic assessment at which a loss of response (i.e., spleen volume no longer reduced by at least 35% from baseline and increased by > 25% from the nadir in spleen volume as measured by MRI or CT) is not observed. If a patient only has one MRI or CT assessment prior to discontinuation or data cutoff, then this will be considered as 'date of last adequate splenic response', too.

Table 8: Computation rules for Duration of the Overall Splenic Response

Situation	Computation of duration of overall splenic response	Censoring (censored/not censored)	Censoring reason
Patients with a splenic response who subsequently had a loss of splenic response.	(Date of loss of splenic response - date of first splenic response + 1) / 7	Not censored	
Patients with splenic response who discontinued from the study prior to loss of splenic response.	(Date of last adequate splenic assessment - date of first splenic response + 1) / 7	Censored	Patients discontinued without loss of splenic response
Event: Death	(Date of death - date of first splenic response +1)/7	Not Censored	
Patients receive a new anti-cancer treatment.	(Date of last splenic assessment prior to date of new anti-cancer treatment - date of first splenic response +1)/7	Censored	New anti-cancer treatment

All other patients with a splenic response.	(Date of last adequate splenic assessment - date of first splenic response + 1) / 7	Censored	Patients without loss of splenic response

15.4.5.2 **Analysis**

Arm/Cohort: arm 1, arm 2, arm 3.

Main analysis

Duration of the overall splenic response will be analysed as detailed below.

- The following will be provided:
  (a) The number and percentage of patients in the ITT set for arms 1, 2 and 3 who had an overall splenic response.

- The number and percentage of patients at risk, with event and with censoring, along with reasons for censoring, will be summarized.
- The distribution of the duration of the overall spleen response will be estimated using the Kaplan-Meier (K-M) method. K-M estimate (%) and 95% confidence limits for the K-M estimate (calculated with Greenwood's formula) will be provided at baseline, every 12 weeks afterwards and at EOT. Median, 25th and 75th percentile for survival time with 95% confidence limits will also be displayed. The confidence limits are constructed using Brookmeyer and Crowley (1982).
- Percent of SVR Responders estimate after 12 weeks, 24 weeks, 36 weeks, 48 weeks, and 60 weeks based on KM estimates and their 95% confidence limits (using Greenwood estimates) will be provided.
- Kaplan-Meier (K-M) method will be presented in tables and displayed graphically.

The K-M statistics will be computed over (a) above. See section 8.5.3 for more details on the K-M estimate.

In addition, K-M estimate of follow-up time for duration of overall splenic response (computed over (a) above) will be provided, where:

- Patients with an overall splenic response who subsequently had a loss of splenic response are censored with their date of loss of splenic response as the censoring date.
- Patients who are censored in the analysis of duration of the overall splenic response above are considered as events, with the date of last adequate splenic assessment as the date of the event.

Then, Q1, median, Q3 and their 95% CI based on the KM estimates (using Brookmeyer and Crowley 1982 method) will be provided.

The reverse K-M method will be presented in tables and displayed graphically.

Sensitivity analysis

A sensitivity analysis will be conducted by adopting the following definition of the duration of the overall splenic response:

Duration of the overall splenic response is defined as the time from when the criterion for splenic response is first met (i.e., a ≥ 35% reduction from baseline spleen volume; see section 6.1.13 for baseline definition) until the time at which a < 35% reduction from baseline in spleen volume as measured by MRI or CT is first documented, or death, whichever comes first.

Site reported spleen volume values will be used for the analysis. If only site-reported spleen parameters are available, apply the formula as provided in section 15.4.1.1.

Duration of the overall splenic response is computed in weeks as specified in Table 8 above, where - for this sensitivity analysis - the following will be applied:

- *Date of first splenic response:* it is the first date at which a ≥ 35% reduction from baseline spleen volume as measured by MRI or CT is observed.

  Date of loss of splenic response: for patients who had reached a ≥ 35% reduction from baseline spleen volume, it is the first date at which the following is observed: spleen volume as measured by MRI or CT is no longer reduced by at least 35% from baseline (i.e., spleen volume reduction < 35%).
- *Date of last adequate splenic assessment:* for patients who had reached a ≥ 35% reduction from baseline spleen volume, it is the date of the last MRI or CT splenic assessment at which a loss of response (i.e., spleen volume reduction < 35% as measured by MRI or CT) is not observed. If a patient only has one MRI or CT assessment prior to discontinuation or data cutoff, then this will be considered as 'date of last adequate splenic response', too.

The same statistical analysis as described for main analysis above will be conducted for the sensitivity analysis.

Subgroup analysis

TWhat follows will be provided.

(1) The duration of the Overall SVR35 will be analysed by the subgroup categories as specified in Table 7 - section 15.4.1.2. The same Kaplan-Meier analysis as specified for the main analysis above will be conducted, with the following exceptions:

- No K-M estimate (%) will be provided at baseline nor every 12 weeks or at EOT. Only median, 25th and 75th percentile for survival time with 95% confidence limits (constructed using Brookmeyer and Crowley, 1982) will be presented.
- The Kaplan-Meier method will only be presented in tables (i.e., not displayed graphically);
- The follow-up time using the reverse KM method will not be assessed for the subgroup analysis.

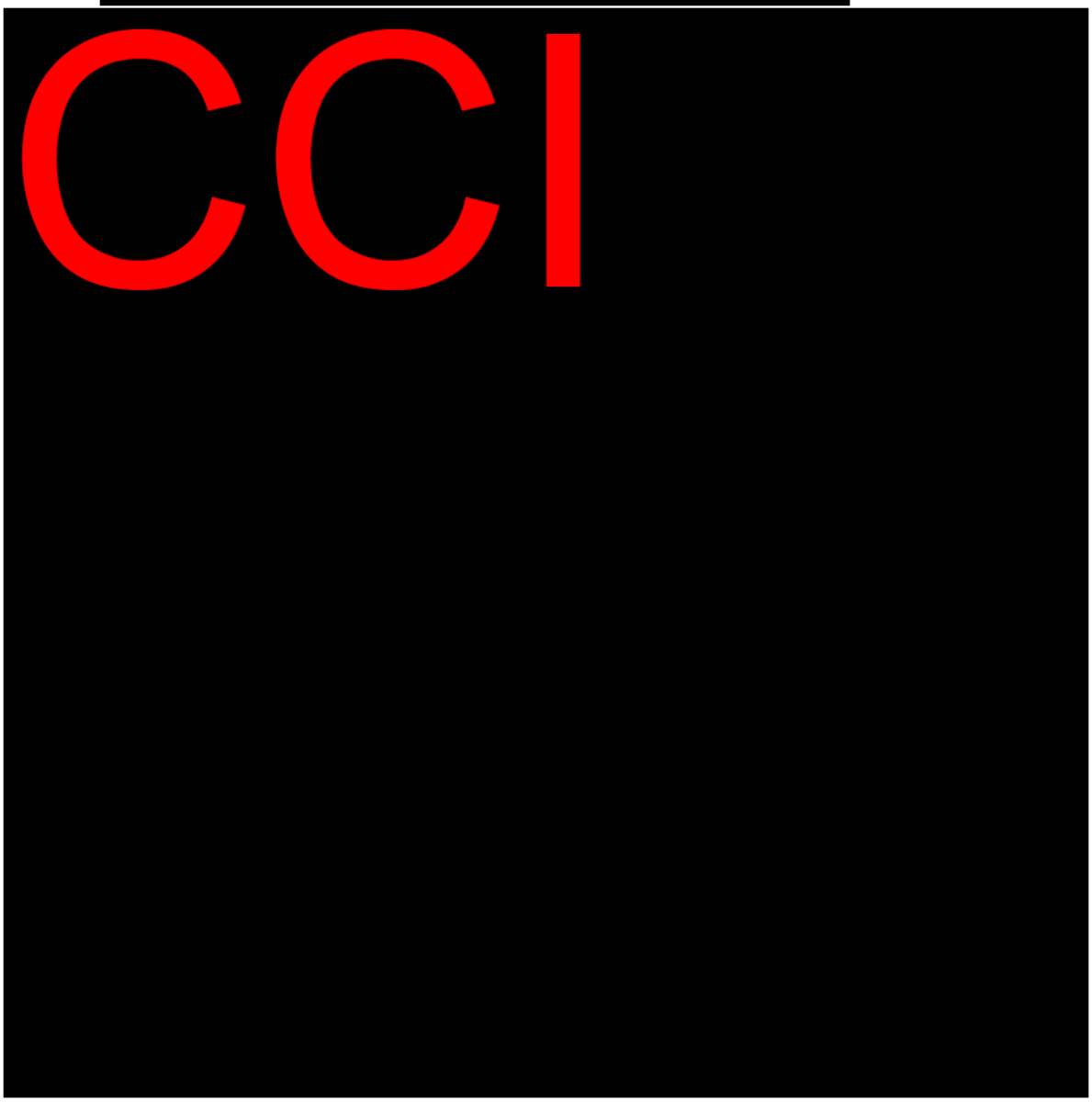
Supportive and additional analysis

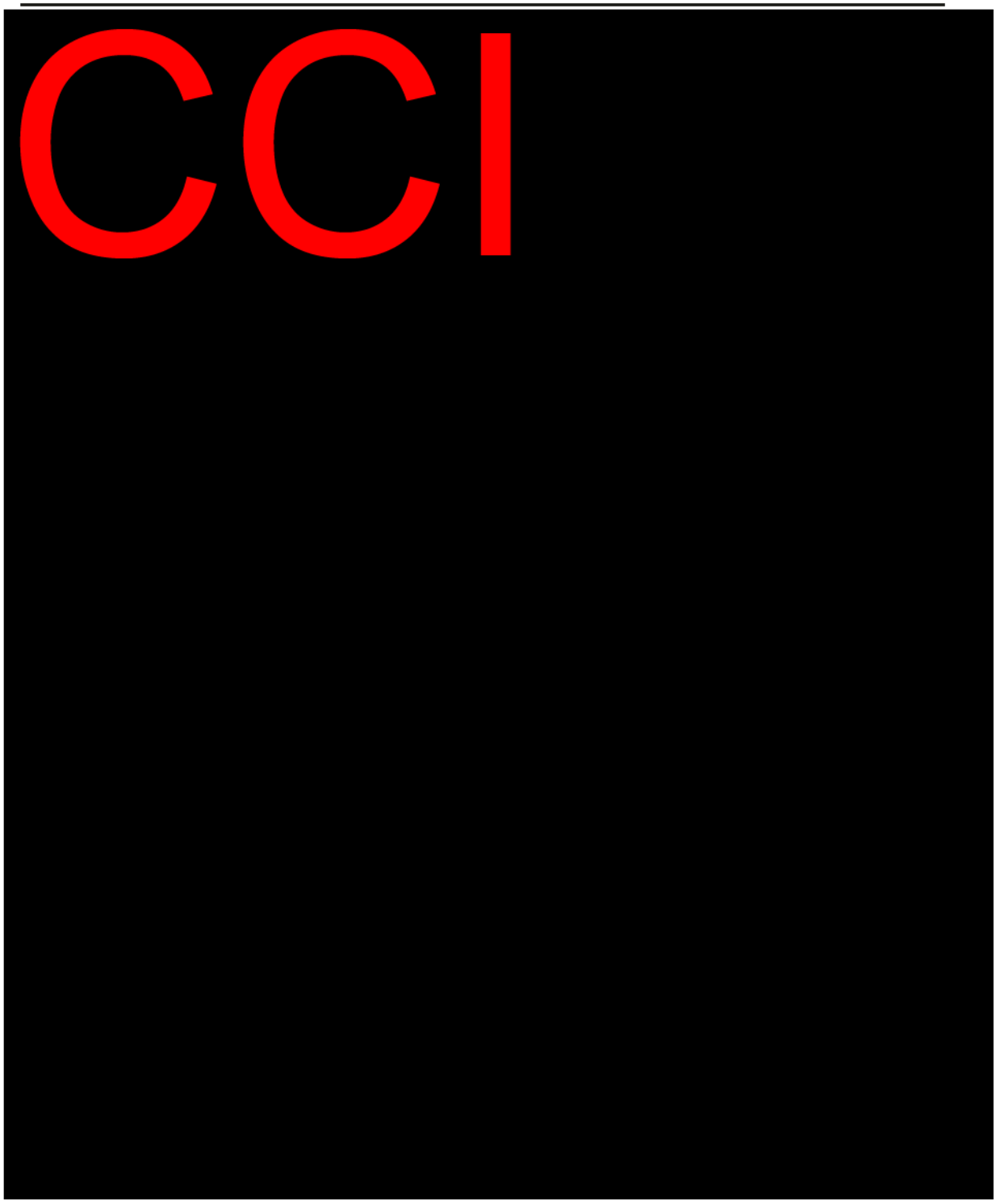
(1) Duration of the Overall Splenic Response on SVR35 responders

The duration of the Overall Splenic Response will be summarized by means of descriptive statistics on Overall SVR35 responders. Data will be presented for each of Arms 1, 2 and 3 and overall. Data for Arms 2 and 3 will also be presented by cohort.

The definition of Overall SVR35 responder is provided in section 15.4.3. In addition, for the purpose of this descriptive analysis conducted on Overall SVR35 responders, the duration of the overall splenic response will be computed as per specifications in Table 8 (section 15.4.5.1), where only information provided in columns "Situation" and "Computation of duration of overall splenic response" will be used.

15.4.6 CCI





15.5 **Symptom assessment**

15.5.1 Total Symptom Score response from the MFSAF at week 24 (MFSAF TSS50)

15.5.1.1 Definition

This is a secondary endpoint for arm 1 (both cohorts 1A and 1B), arm 2 (cohorts 2A and 2B) and arm 3. Not applicable for arm 4.

The Total Symptom Score response (TSS50) is defined as a $\geq$ 50% decrease from baseline to week 24 (Cycle 9, Day 1) in the 7-day average TSS as measured by the Myelofibrosis Symptom Assessment Form (MFSAF) version 4.0 - see section 6.1.14 for baseline definition.

The MFSAF assessment is completed every day for 7 days prior to Day 1 of each cycle, including during the screening period. For the screening period, the 7 days prior to Cycle 1 Day 1 (C1D1, section 6.1.6) are preferred, but MFSAF scores collected for 7 consecutive days at any time during the 28 days screening period will be accepted. The MFSAF uses a 24-hour recall format and asks the patient to rate the severity of each symptom (i.e., fatigue, night sweats, pruritus, abdominal discomfort, pain under the ribs on the left side, early satiety, and bone pain) at its worst during the past 24 hours. The MFSAF asks the patient to report symptom severity at its worst for each of the 7 items on a 0 (Absent) to 10 (Worst Imaginable) numeric rating scale. Data collected for the MFSAF screening assessment are recorded in the eCRF page "Myelofibrosis Symptom Assessment (MFSAF) v4.0 (Scr) (MFSAF)". Data collected in the 7-day interval prior to day 1 of each cycle are recorded in the eCRF page "Myelofibrosis Symptom Assessment (MFSAF) v4.0 (MFSAF_1)".

The TSS for the 24-hour recall (i.e., daily diary) format of the MFSAF v4.0 is the sum of the 7 individual item responses on the 0-10 scale, with a possible total daily score that may range from 0 to 70. All 7 items must be completed for a daily TSS to be computed.

The weekly TSS is calculated by averaging the 0-to-70 daily scores collected over the 7-day interval during screening and weekly based on Table 18.

Whenever needed, the weekly TSS for each of the 7 items of the MF-SAF will be obtained by averaging the 0-to-10 daily rates of each item collected over the 7-day interval during screening and weekly based on Table 18.

15.5.1.2 Analysis

Arm/Cohort: arm 1, arm 2, arm 3.

See section 6.1.14 for definition of baseline TSS. Details on the study week and analysis visit windows for the MFSAF TSS are provided in sections 22.2 and 22.3, respectively. See section 21.1 for handling of missing TSS values.

Main analysis

The MF-SAF TSS50 at week 24 will be analyzed as detailed below.

- The following will be provided:

a. The number and percentage of patients in the ITT set for arms 1, 2 and 3 evaluable for TSS50 at week 24 (see table below);
b. The number and percentage of patients in the ITT set for arms 1, 2 and 3 non-evaluable for TSS50 at week 24, along with reasons for non-evaluability (see table below).

- The number and percentage of patients achieving a ≥ 50% reduction in the MFSAF TSS at week 24 will be summarized; exact 95% confidence limits of the binomial distribution will be provided. This rate will be computed over (a) above. Patients will be considered as responders/non-responders based on what follows:

    - Patients achieved ≥ 50% reduction from baseline in TSS at week 24: responders.
    - Patients did not achieve ≥ 50% reduction from baseline in TSS at week 24: non-responders.
    - Patients have TSS = 0/missing at baseline and discontinued (based on the date of end of treatment) before week 19 (Day 127): non-responders.
    - Patients have non-missing/non-zero baseline TSS and week 24 TSS is missing per visit window/imputation: non-responders.

- The percent change from baseline to week 24 in TSS from the MFSAF score will be summarized and it will also be presented using a waterfall plot. The waterfall plot will display one bar for each patient included in the analysis and will be sorted in descending order.
- The percent change from baseline to the best post-baseline result in the MFSAF TSS will be summarized.

- Absolute values and changes from baseline to each post-baseline assessment in TSS from the MFSAF will be summarized. A listing will also be produced.

Note: the changes from baseline as listed above will be computed if both baseline and the post-baseline assessment(s) in TSS are available. The summaries will also include the number of not-available data for each assessment under scrutiny (i.e., baseline, post-baseline).

A listing of non-evaluable patients for TSS50 at week 24 with reasons for non-evaluability (see details below) will be generated.

The table below describes the criteria for patients' evaluability/non-evaluability for TSS50 at week 24, as well as the possible reasons for non-evaluability.

Criterion	**(Non-)evaluability**	**Rationale for non-evaluability**	**Reason for non-evaluability**
For patients on treatment at corresponding timepoint of analysis			
Have non-zero/non-missing TSS at baseline, and have TSS at week 24.	Evaluable		

Have TSS=0 or missing at baseline.	Non-evaluable	(Ongoing at cutoff date with) baseline MF-SAF TSS = 0 or missing. Percent change from baseline cannot be computed.	Non-evaluable baseline TSS.
Have non-zero/non-missing TSS at baseline, but have no TSS at week 24 (based on study week) or beyond.	Non-evaluable	(Ongoing at cutoff date with) no MF-SAF TSS at week 24 or beyond. Week 24 TSS may not happen yet or it is not available per visit window or imputation.	Not-available TSS value at week 24
For discontinued patients			
Have non-zero/non-missing TSS at baseline, and have TSS at week 24.	Evaluable		
Have non-zero/non-missing TSS at baseline, and have missing TSS at week 24.	Evaluable		
Have TSS=0 or missing at baseline and discontinue (based on the date of the end of treatment) before week 19 (Day 127).	Evaluable		
Have TSS=0 or missing at baseline and discontinue (based on the date of the end of treatment) on/after week 19 (Day 127).	Non-evaluable	Have baseline MF-SAF TSS = 0/missing and discontinue on/after week 19. Percent change from baseline cannot be computed.	Non-evaluable baseline TSS.

Sensitivity Analysis for main analyses

(1) A sensitivity analysis will be conducted on the MFSAF TSS50 at week 24 which consists of computing the weekly TSS by applying the following rule: both baseline and post-baseline TSS values will be calculated based on at least 4 non-missing daily total symptom scores for the corresponding week (i.e., baseline, post-baseline). The weekly TSS will be considered as missing if less than 4 daily total symptom scores are available for the week at stake.

The statistical analyses to be conducted are the same as described for the main analysis.

(2) TSS0, TSS15, TSS35, TSS75

Symptom assessment through the MF-SAF v4.0 will be evaluated by looking at several thresholds in the weekly TSS (see section 15.5.1.1 for computation of TSS), as follows:

- **TSS0**, defined as a ≥ 0 % decrease from baseline to week 24 (Cycle 9, Day 1) in the 7-day average TSS as measured by the MFSAF v 4.0.
- **TSS15,** defined as a ≥ 15 % decrease from baseline to week 24 (Cycle 9, Day 1) in the 7-day average TSS as measured by the MFSAF v4.0.
- **TSS35,** defined as a ≥ 35 % decrease from baseline to week 24 (Cycle 9, Day 1) in the 7-day average TSS as measured by the MFSAF v4.0.
- **TSS75,** defined as a ≥ 75 % decrease from baseline to week 24 (Cycle 9, Day 1) in the 7-day average TSS as measured by the MFSAF v4.0.

See section 6.1.14 for baseline definition and main analysis for patients' evaluability/non-evaluability.

TSS0, TSS15, TSS35 and TSS75 will be analysed separately as detailed below.

- The following will be provided:
    a. The number and percentage of patients in the ITT set for arms 1, 2 and 3 evaluable for TSS0/15/35/75 at week 24;
    b. The number and percentage of patients in the ITT set for arms 1, 2 and 3 non-evaluable for TSS0/15/35/75 at week 24, along with reasons for non-evaluability.

- The number and percentage of patients achieving a ≥ 0/15/35/75 % reduction (for, respectively, TSS0, TSS15, TSS35 and TSS75) in the MFSAF TSS at week 24 will be summarized; exact 95% confidence limits of the binomial distribution will be provided. The rate will be computed over (a) above. Patients will be considered as responders/non-responders as follows:

    - Patients achieved ≥ 0/15/35/75% reduction from baseline in TSS at week 24: responders.
    - Patients did not achieve ≥ 0/15/35/75% reduction from baseline in TSS at week 24: non-responders.
    - Patients have TSS = 0/missing at baseline and discontinued (based on the date of end of treatment) before week 19 (Day 127): non-responders.
    - Patients have non-missing/non-zero baseline TSS and week 24 TSS is missing per visit window/imputation: non-responders.

Additionally, subgroup analyses (2), (3), (4) and (5) as described below (i.e., for the subgroup analysis on MF-SAF TSS50) will also be conducted on TSS0, TSS15, TSS35 and TSS75. For (3), (4) and (5), the same analysis as listed above will be performed.

(3) The same analyses as those listed below will be conducted on the PPS analysis set:

- Main analysis,
- Sensitivity analysis (1),
- Supportive and Additional analysis (see below),
- Subgroup Analyses (1)-to-(5) (see below).

(4) Last Observation Carried Forward (LOCF) imputation on missing values for the MFSAF TSS

LOCF imputation methodology will be applied for missing values of the MFSAF TSS at weeks 12, 24, 36, 48, 60, 72 and at every 12 weeks thereafter, after the implementation of the study weeks and the visit windows for the MFSAF TSS (sections 22.2 and 22.3, respectively). Therefore, for each week under scrutiny, if a patient does not have a MFSAF TSS score even considering the range of +/-6 weeks for the lower and upper bounds of the visit windows as per section 22.3, this missing value will be imputed with the last non-missing available TSS value for that patient - i.e., the last non-missing TSS value is carried forward to the time-point under scrutiny.

The following will be summarized using LOCF-imputed data, by arm/cohort and overall:

- Absolute and percent change from baseline to week 24 in TSS from the MFSAF v4.0;
- Absolute and percent change from baseline to weeks 12, 36, 48, 60, 72 and every 12 weeks thereafter.

In addition, the percent change in the MFSAF TSS from baseline to week 24 will be graphically reported using a forest plot for the subgroup categories as specified in Table 7 - section 15.4.1.2 For each subgroup category, as well as for the overall ITT set the forest plot will display the mean percent change in TSS from baseline to week 24.

Supportive and Additional Analysis

A set of additional analyses will be conducted on the TSS50 as measured by the MFSAF v4.0 by considering additional post-baseline assessments, namely TSS50 at week 12, week 36, week 48, week 60, week 72 and every 12 weeks thereafter. These are defined below.

The criteria for patients' (non-)evaluability, as well as the possible reasons for non-evaluability, are specified in Table 9 below.

1. *MFSAF TSS50 at week 12*

This is defined as a ≥ 50% decrease from baseline to week 12 in 7-day average TSS as measured by the MFSAF v4.0.

2. MFSAF TSS50 at week 36

This is defined as a ≥ 50% decrease from baseline to week 36 in 7-day average TSS as measured by the MFSAF v4.0.

3. MFSAF TSS50 at week 48

This is defined as a ≥ 50% decrease from baseline to week 48 in 7-day average TSS as measured by the MFSAF v4.0.

4. MFSAF TSS50 at week 60

This is defined as a ≥ 50% decrease from baseline to week 60 in 7-day average TSS as measured by the MFSAF v4.0.

5. MFSAF TSS50 at week 72 and every 12 weeks thereafter

The MFSAF TSS50 at week 72 is defined as a ≥ 50% decrease from baseline to week 72 in 7-day average TSS as measured by the MFSAF v4.0.

The MFSAF TSS50 at every 12 weeks after week 72 is defined as a ≥ 50% decrease from baseline to the given week (i.e., week 84, week 96, week 108, etc.) in the 7-day average TSS as measured by the MFSAF v4.0.

The MFSAF TSS50 at weeks 12, 36, 48, 60, 72 and every 12 weeks thereafter will be analysed, separately for each week under scrutiny, as described below.

- The following will be provided:

    a. The number and percentage of patients in the ITT set for arms 1, 2 and 3 evaluable for TSS50 at the given week (i.e., 12, 36, 48, 60, 72 and every 12 weeks thereafter); see table below for evaluability criteria;
    b. The number and percentage of patients in the ITT set for arms 1, 2 and 3 non-evaluable for TSS50 at the given week (i.e., 12, 36, 48, 60, 72 and every 12 weeks thereafter), along with reasons for non-evaluability (see table below for details on non-evaluability).

- The number and percentage of patients achieving a ≥ 50% reduction in the MFSAF TSS at the given week will be summarized; exact 95% confidence limits of the binomial distribution will be provided. This rate will be computed over (a) above. Patients will be considered as responders/non-responders based on what follows:

    - Patients achieved ≥ 50% reduction from baseline in TSS at the given week (i.e., 12, 36, 48, 60, 72 and every 12 weeks thereafter): responders.
    - Patients did not achieve ≥ 50% reduction from baseline in TSS at the given week: non-responders.
    - Patients have TSS = 0/missing at baseline and discontinued (based on the date of end of treatment) before:
        - For TSS50 at week 12: week 7 (Day 43): non-responders.
        - For TSS50 at week 36: week 31 (Day 211): non-responders.
        - For TSS50 at week 48: week 43 (Day 295): non-responders.
        - For TSS50 at week 60: week 55 (Day 379): non-responders.
        - For TSS50 at week 72: week 67 (Day 463): non-responders.

        - For TSS50 at every 12 weeks after week 72:
          The lower bound of the analysis visit window of the week under scrutiny (see Table 19 in section 22.3): non-responders.
          For example, for TSS50 at week 84, patients with baseline TSS = 0 or missing and who discontinued (based on the date of end of treatment) before Day 547 (week 79) will be considered as non-responders.

- Patients have non-missing/non-zero baseline TSS and TSS at the given week (i.e., 12, 36, 48, 60, 72 and every 12 weeks thereafter) is missing per visit window/imputation: non-responders.

- The percent change from baseline to week 12/36/48/60, 72 and every 12 weeks thereafter in TSS from the MFSAF score will be summarized and it will also be presented using a waterfall plot. The waterfall plot will display one bar for each patient included in the analysis and will be sorted in descending order. The percent change from baseline will be computed only when both baseline and the post-baseline assessment are available. The summaries will also include the number of not-available data for each time-point under scrutiny (i.e., baseline/post-baseline).

In addition, sensitivity analyses (1) and (3) as described for the sensitivity analysis of the MFSAF TSS50 at week 24 will be conducted for (1)-to-(4) above. Sensitivity analysis (1) will be conducted for (5) above (i.e., MFSAF TSS50 at week 72 and every 12 weeks thereafter).

Table 9: Patients' evaluability for MFSAF TSS50 at week 12, 36, 48, 60, 72 and every 12 weeks thereafter

Criterion	(Non-)evaluability	Rationale for non-evaluability	Reasons for non-evaluability
For patients on treatment at corresponding timepoint of analysis			
Have non-zero/non-missing TSS at baseline, and have TSS at the given week (i.e., 12, 36, 48, 60, 72 and every 12 weeks thereafter).	Evaluable		
Have TSS=0 or missing at baseline.	Non-evaluable	(Ongoing at cutoff date with) baseline MF-SAF TSS = 0 or missing. Percent change from baseline cannot be computed.	Non-evaluable baseline TSS.
Have non-zero/non-missing TSS at baseline, but have no TSS (based on study week) at : -For TSS50 at week 12: week 7 (Day 43) or beyond. -For TSS50 at week 36: week 31 (Day 211) or beyond. -For TSS50 at week 48: week 43 (Day 295) or beyond.	Non-evaluable	(Ongoing at cutoff date with) no MF-SAF TSS at: - Week 7 or beyond (for TSS50 at week 12 only). - Week 31 or beyond (for TSS50 at week 36 only). - Week 43 or beyond (for TSS50 at week 48 only). - Week 55 or beyond (for TSS50 at week 60 only). - Week 67 (for TSS50 at week 72).	Not-available TSS value at week 12/36/48/60/72/n+12*. *<u>*Note*</u>: depending on the week under scrutiny.

-For TSS50 at week 60: week 55 (Day 379) or beyond. - For TSS50 at week 72: week 67 (Day 463). - For TSS50 at every 12 weeks after week 72: the lower bound of the analysis visit window of the week under scrutiny (see Table 19 in section 22.3). For example for TSS50 at week 84, this would be Day 547 (week 79).		- Week n* (for TSS50 at every 12 weeks after week 72). *where week n is the week under which the lower bound of the analysis visit window of the week under scrutiny falls (e.g., week 79 for TSS50 at week 84). TSS for the weeks under scrutiny may not happen yet or it is not available per visit window or imputation.	
For discontinued patients			
Have non-zero/non-missing TSS at baseline, and have TSS at the given week (i.e., 12, 36, 48, 60, 72 and every 12 weeks thereafter).	Evaluable		
Have non-zero/non-missing TSS at baseline, and have missing TSS at the given week.	Evaluable		
Have TSS=0 or missing at baseline and discontinue (based on the date of the end of treatment) before: -For TSS50 at week 12: week 7 (Day 43). -For TSS50 at week 36: week 31 (Day 211). -For TSS50 at week 48: week 43 (Day 295). -For TSS50 at week 60: week 55 (Day 379). - For TSS50 at week 72: week 67 (Day 463) - For TSS50 at every 12 weeks after week 72: the lower bound of the analysis visit window of	Evaluable		

the week under scrutiny (see Table 19 in section 22.3). For example, for TSS50 at week 84, this would be Day 547 (week 79).			
Have TSS=0 or missing at baseline and discontinue (based on the date of the end of treatment) on/after: -For TSS50 at week 12: week 7 (Day 43). -For TSS50 at week 36: week 31 (Day 211). -For TSS50 at week 48: week 43 (Day 295). -For TSS50 at week 60: week 55 (Day 379). - For TSS50 at week 72: week 67 (Day 463) - For TSS50 at every 12 weeks after week 72: the lower bound of the analysis visit window of the week under scrutiny (see Table 19 in section 22.3). For example, for TSS50 at week 84, this would be Day 547 (week 79).	Non-evaluable	Have baseline MF-SAF TSS = 0/missing and discontinue on/after: - Week 7 (for TSS50 at week 12 only). - Week 31 (for TSS50 at week 36 only). - Week 43 (for TSS50 at week 48 only). - Week 55 (for TSS50 at week 60 only). - Week 67 (for TSS50 at week 72) - Week n* (for TSS50 at every 12 weeks after week 72). *where week n is the week under which the lower bound of the analysis visit window of the week under scrutiny falls (e.g., week 79 for TSS50 at week 84). Percent change from baseline cannot be computed.	Non-evaluable baseline TSS.

Subgroup Analysis

The subgroup analyses as detailed below will be performed.

(1) The percent reduction in TSS as assessed from the MFSAF v4.0 from baseline to week 24 will be graphically reported using a forest plot for the subgroup categories as specified in Table 7 - section 15.4.1.2 For each subgroup category, as well as for the overall ITT set (see section 15.4.1.2 for patients' evaluability), the forest plot will display the mean percent reduction in TSS from baseline to week 24 as well as the corresponding 95% exact confidence interval

(2) The total symptom score response rate at week 24 (MFSAF TSS50) will be graphically displayed with a forest plot for the subgroup categories as specified in Table 7 - section 15.4.1.2. For each subgroup category, as well as for the overall ITT set, the forest plot will show the MFSAF TSS50 rate at week 24 together with the corresponding 95% exact confidence interval.

(3) MFSAF TSS50 at week 24 will be analyzed in the following subgroup of patients:

- For arms 1 and 2: Patients with at least 2 measurable symptoms in the baseline MFSAF v4.0 (score ≥ 1).
- For arm 3: Patients with at least 2 measurable symptoms in the baseline MFSAF v4.0 (i.e., weekly averaged score ≥ 3 in the MFSAF v4.0 assessment) or with a total score ≥ 10 (i.e., weekly averaged) in the baseline MFSAF v4.0 assessment.

(4) MFSAF TSS50 at week 24 will be analyzed in the following subgroup of patients:

- Patients with baseline TSS as measured from the MFSAF: > 10 and ≤ 10.

(5) Arm 1: TSS50 at week 24 by Prior Response to JAK inhibitor (JAKi)

TSS50 at week 24 will also be analyzed on Arm 1 only based on the prior response to JAKi subgroups as defined in subgroup analysis (3) for SVR35 at week 24, section 15.4.1.2.

(6) Arm 1 and Arm 2: TSS50 at week 24 by line of Prior JAKi Therapy

TSS50 at week 24 will also be analyzed on Arm 1 and Arm 2 based on the subgroups of patients with 1 line or prior JAKi therapy and with > 1 line of prior JAKi therapy, as defined in subgroup analysis (4) for SVR35 at week 24, section 15.4.1.2.

For subgroup analyses (3), (4), (5) and (6), the same analysis as for the MFSAF TSS50 main analysis will be conducted.

(7) MFSAF TSS50 at every 12 weeks by subgroups

The MFSAF TSS50 will be summarized by the subgroup categories as specified in Table 7 - section 15.4.1.2, for Arms 1, 2 and 3, at week 24 as well as at the additional time-points (1)-to-(5) as specified in *Supportive and Additional Analysis* above (i.e., weeks 12, 36, 48, 60, 72 and every 12 weeks thereafter).

For each time-point and subgroup:

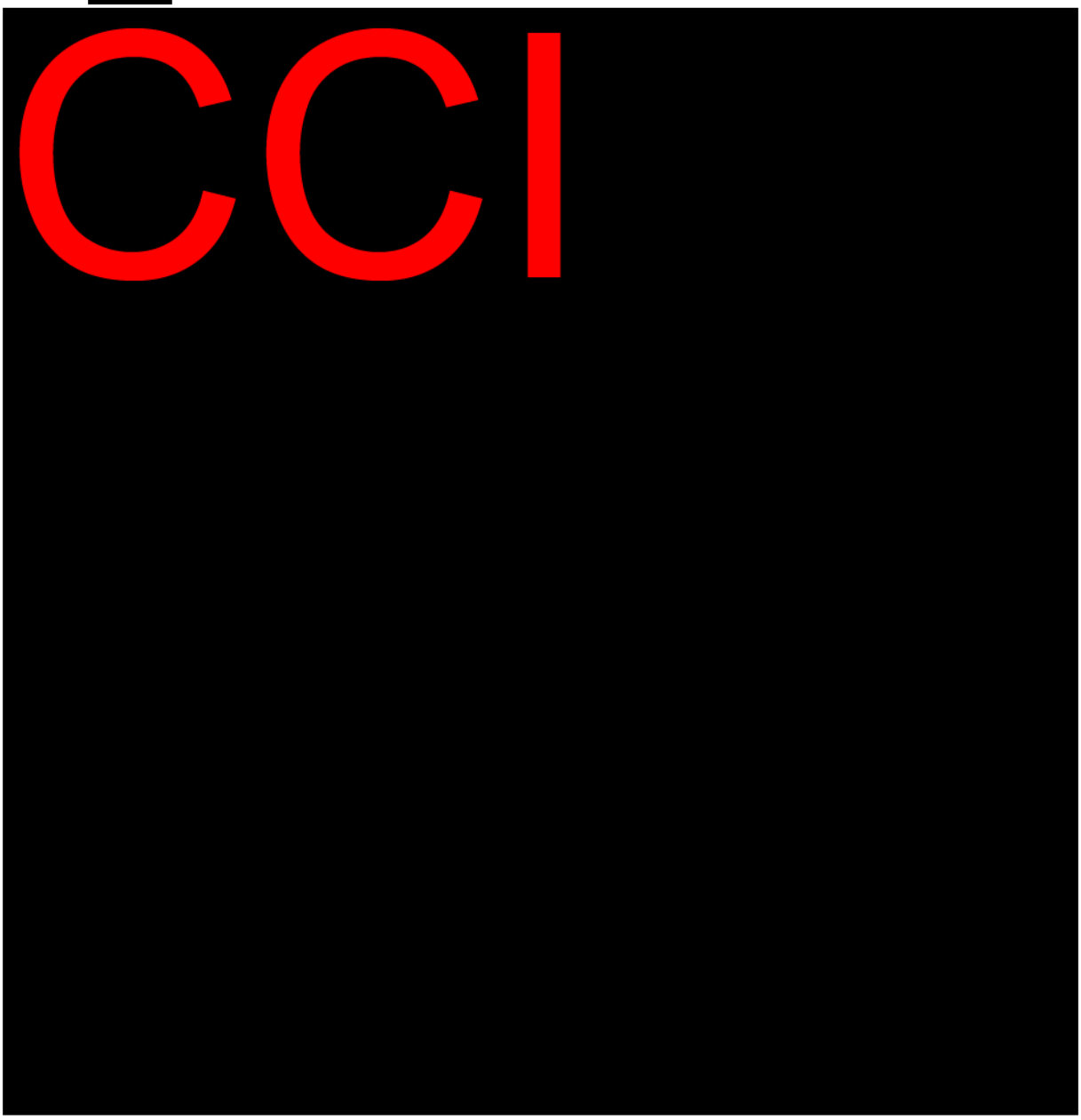
- The following will be provided:
    a. The number and percentage of patients in the ITT set evaluable for the MFSAF TSS50 at the given week.

- The number and percentage of patients achieving $\geq 50\%$ decrease from baseline in the total symptom score as measured by the MF-SAF v4.0 at the given week will be summarized; exact 95% confidence limits of the binomial distribution will be provided. The rate will be computed over (a) above.

For patients' (non-)evaluability for the MFSAF TSS50 at the given week and for patients' classification as responders/non-responders, see the corresponding specifications provided for each of the week under scrutiny (section 15.5.1.2 for MFSAF TSS50 at week 24; *Supportive and Additional Analysis* above for MFSAF TSS50 at the additional time-points - i.e., weeks 12/36/48/60/72 and every 12 weeks thereafter).

Data will be summarized by arm/cohort and overall.

15.5.2 CCI

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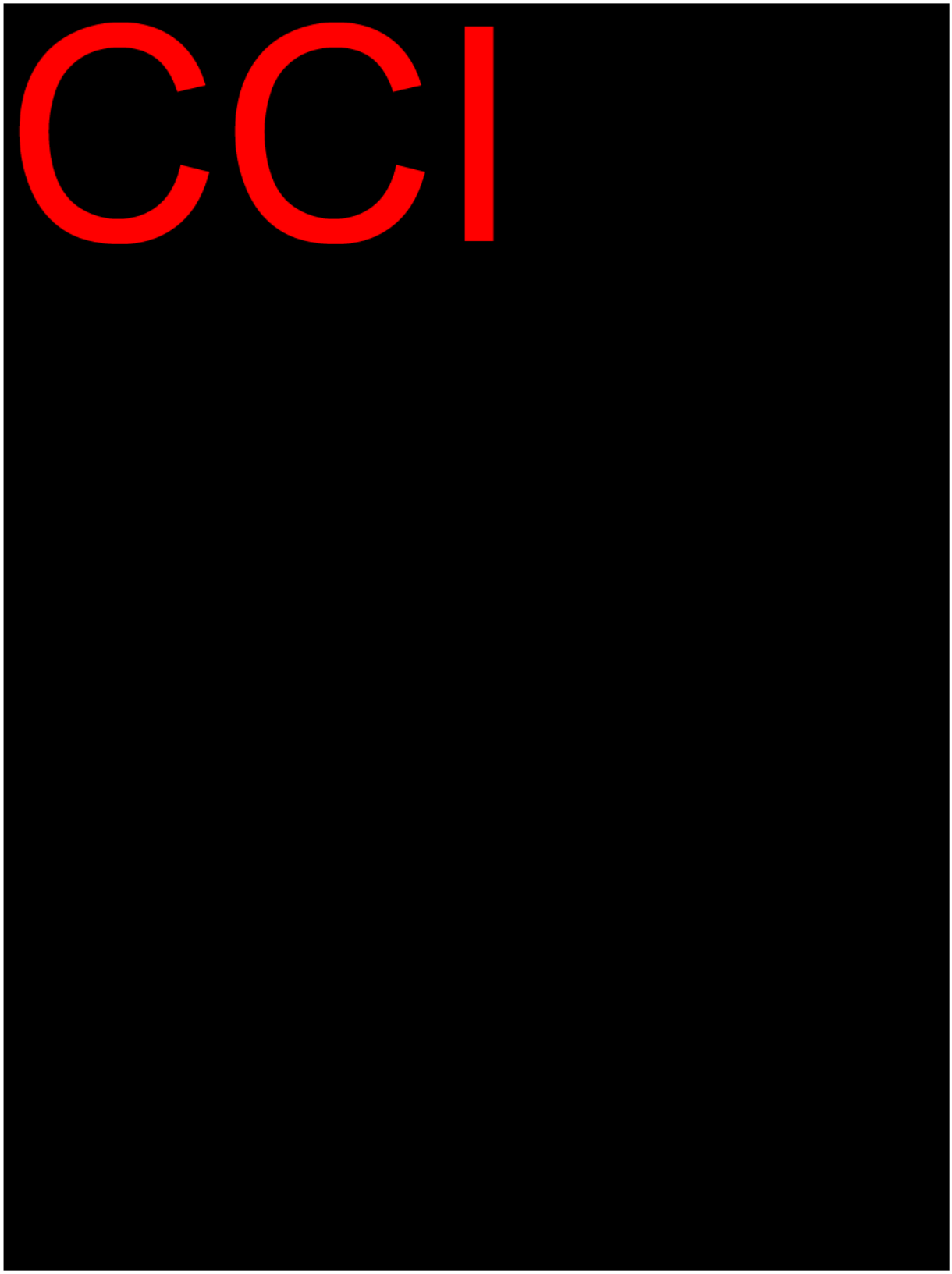
15.5.4 CCI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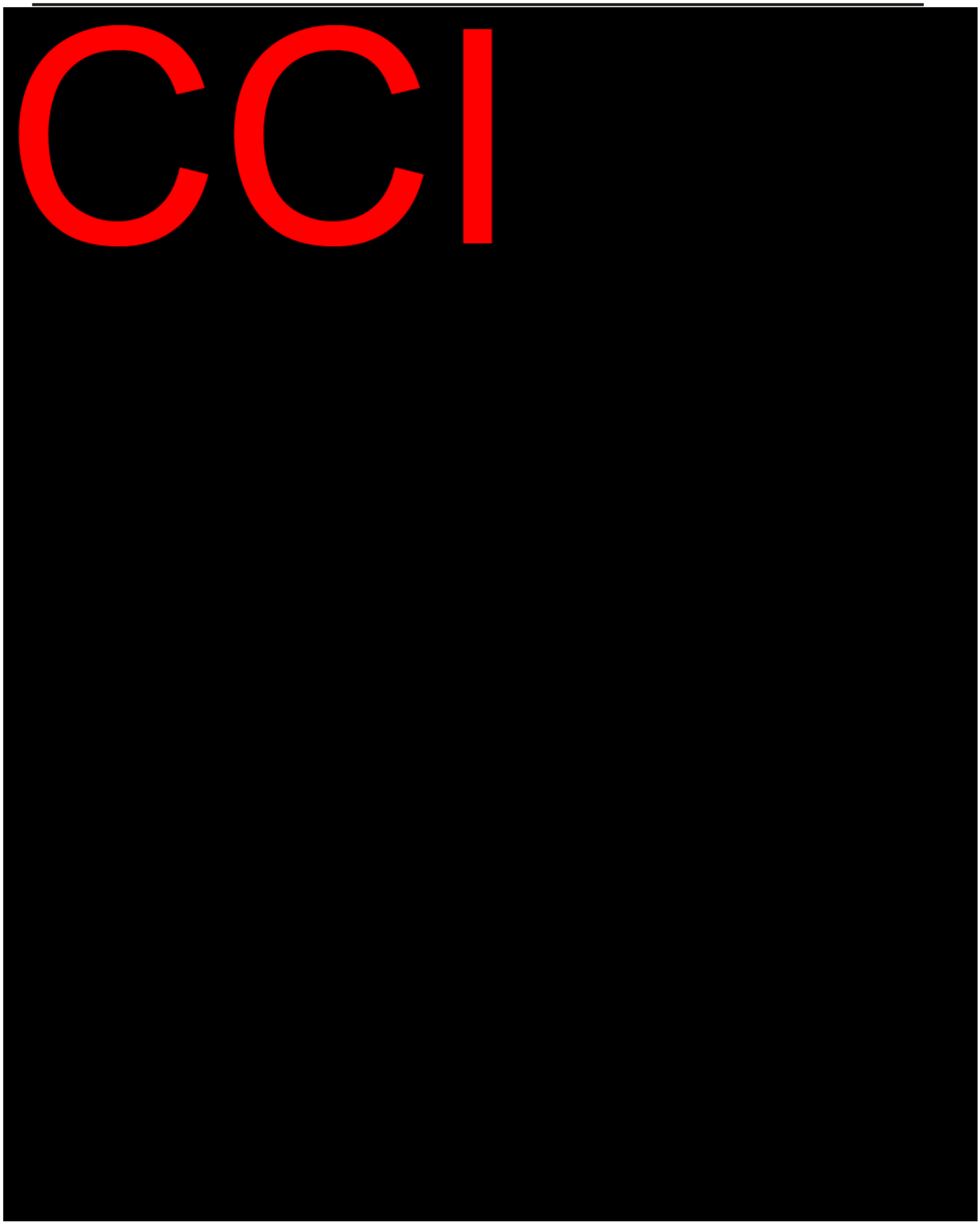
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15.5.5 MF-SAF TSS as continuous endpoint

15.5.5.1 Comparison of mean percent changes using MMRM

For Arm 3 only, the mean percent change from baseline to each assessment in the MF-SAF TSS (see section 15.5.1.1 for the TSS computation) will be analyzed using Mixed Model Repeated Measures (MMRM) statistics. This analysis will be conducted on the ITT set.

A MMRM model will be applied to test the following null hypothesis H0: the mean percent on the changes from baseline in the MF-SAF TSS does not differ over time.

The MMRM model will have the percent change from baseline to each visit up to week 60 in the MF-SAF TSS as a continuous dependent variable, visit as a fixed factor and baseline MF-SAF TSS, age, and MF subtype as covariates. Hence, the modelwill specify no patient-level random effects, but will model instead the correlation within the repeated measure over time by specifying that the residual errors are correlated. In particular, to reduce biases due to model misspecification, the residual errors are assumed to be from a multivariate normal distribution with an unstructured covariance matrix.

The p-values for the type 3 tests of fixed effect will be reported. The LS-means for each visit under scrutiny along with standard error and 95% Confidence Interval of the LS-means will be reported as well.

The model will be fitted in SAS using PROC MIXED, with type = UN; the noint option will be included

Note: for the fixed factor Visit, visits up to week 60 will be considered in the model.

Additionally, the following set of analyses will be conducted:

For each of the 7 items of the MF-SAF (i.e.,fatigue, night sweats, pruritus, abdominal discomfort, pain under the ribs on the left side, early satiety, bone pain), separate MMRM models will be conducted. These models will test the null hypothesis H0 that the mean percent on the change from baseline in the MF-SAF TSS for each of the 7 items does not differ over time. The fixed factor as well as the covariates of these models will be the same as detailed above for the main MMRM model. The continuous dependent variable(s) will be the percent change from baseline to each visit up to week 60 in the TSS for each of the 7 items included in the MF-SAF (i.e., the TSS for fatigue, the TSS for night sweats, etc.).

See section 15.5.1.1 for details on the MF-SAF assessment and computation of the TSS for each item.

Finally, the following will be provided:

- One boxplot of percent changes in the MF-SAF TSS scores from baseline over time;
- One boxplot of absolute changes in the MF-SAF TSS scores from baseline over time;
- Separate boxplots per item (i.e., fatigue, night sweats, pruritus, abdominal discomfort, pain under the ribs on the left side, early satiety, bone pain) of the percent changes in the MF-SAF TSS of each item from baseline over time;
- Separate boxplots per item (i.e., fatigue, night sweats, pruritus, abdominal discomfort, pain under the ribs on the left side, early satiety, bone pain) of the absolute changes in the MF-SAF TSS of each item from baseline over time.

15.5.5.2 Estimate of median changes using Hodges-Lehmann estimates

For each visit, the estimate of median changes from baseline to each assessment in the MF-SAF TSS will be performed using Hodges-Lehmann estimates with PROC npar1way in SAS. The location shift and exact 95% confidence limits will be reported. Median changes from baseline will be computed only when both baseline and post-baseline assessment are available. The summary will also report the number of missing data at baseline and at each post-baseline assessment.

The same as above will be conducted also for the TSS of each item of the MF-SAF.

15.5.5.3 **Mixed Model Repeated Measures statistics on 28-days averaged MFSAF TSS**

A mixed model repeated measures (MMRM) will be used to analyze the mean percent change from baseline at every 4 weeks in the MFSAF TSS as derived within an interval of 28 days (MFSAF TSS $_{28\ Days}$). This analysis will be conducted only on Arm 3 and only on the ITT set. Details are given in what follows.

Derivation of the MFSAF TSS $_{28\ Days}$

The MFSAF TSS $_{28\ Days}$ consists of a different computation of the MFSAF TSS that is based on the average of the non-missing daily total symptom scores over an interval of 28 consecutive days (i.e., 4 weeks).

To compute this: study weeks for TSS as described in section 22.2 are derived. Afterwards, the MFSAF TSS $_{28\ Days}$ is calculated as the average of non-missing daily total symptom scores over 4 consecutive weeks.

The 28-day averaged TSS data will then be mapped to an appropriate analysis visit as specified in section 22.3.

Note: the derivation of TSS based on the 28-day interval is valid for post-baseline assessments of the TSS. For baseline, the definition provided in section 6.1.14 applies for this analysis as well, and baseline TSS is therefore derived based on the average of the non-missing daily total symptom scores over 7 days.

MMRM model statistics on the MFSAF TSS $_{28\ Days}$

A MMRM model will be applied to test the following null hypothesis H0: the mean percent on the changes from baseline in the MFSAF TSS $_{28\ Days}$ does not differ over time.

The MMRM model will have the percent change from baseline at every 4 weeks in the MFSAF TSS $_{28\ Days}$ as a continuous dependent variable, visit as a fixed factor and the following covariates:

- baseline MFSAF TSS,
- baseline DIPSS (Intermediate-1 risk, Intermediate-2 risk,. High risk),
- baseline platelet count (> 200 10^9/L, $\leq$ 200 10^9/L),
- baseline spleen volume (> 1800 cc, $\leq$ 1800 cc).

Hence, the modelwill specify no patient-level random effects, but will model instead the correlation within the repeated measure over time by specifying that the residual errors are correlated. In particular, to reduce biases due to model misspecification, the residual errors are assumed to be from a multivariate normal distribution with an unstructured covariance matrix.

The p-values for the type 3 tests of fixed effect will be reported. The LS-means for each visit under scrutiny along with standard error and 95% Confidence Interval of the LS-means will be reported, too.

The model will be fitted in SAS using PROC MIXED, with type = UN; the noint option will be included.

15.5.6 Total Symptom Score response from the MPN-SAF at week 24 (MPN-SAF TSS50)

15.5.6.1 Definition

This is a secondary endpoint for Arm 4. Not applicable for arms 1, 2 and 3.

The Total Symptom Score response as measured by the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF TSS50) is defined as a ≥ 50% decrease from baseline to week 24 (Cycle 9, Day 1) in the 7-day average TSS of the MPN-SAF (i.e., completed by patients on day 15 to 21 of Cycle 8; see below for more details) - see section 6.1.14 for baseline definition.

The MPN-SAF assessment is completed during the screening period every day for the 7 days prior to C1D1 (section 6.1.6) (preferred) - or alternatively for any 7 consecutive days during the 28 days screening period. Afterwards, it is collected from day 15 to day 21 of Cycles 1, 2, 4, 8, and every 4 cycles thereafter (see section 23 for the schedule of assessments). The MPN-SAF uses a 24-hour recall format and asks the patients to rate the severity of each symptom (i.e., 18 items, including fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers) at its worst in the past 24 hours. For each of the 18 items, scoring ranges from 0 (absent) to 10 (worst imaginable), and the total daily score is the sum of all individual scores (i.e., 0-to-180 numeric rating scale). All items must be completed for a daily TSS to be computed.

Data collected for the MPN-SAF screening assessment are recorded in the eCRF page "MPN-SAF A10 (Screening) (MA_1)". Data collected from day 15-to-21 of the relevant cycles are recorded in the eCRF page "MPN-SAF A10 (MA_2)".

The MPN-SAF 7-day TSS is calculated by averaging the 0-to-180 daily scores collected over the 7-day interval during screening, and over any 7-day interval prior to Day 1 of the next cycle (see above).

15.5.6.2 Analysis

Arm/Cohort: Arm 4.

See: section 6.1.14 for baseline definition of the MPN-SAF TSS50; sections 22.2 and 22.3 for, respectively, study week definition and visit windows; section 21.1 for imputation rules.

Main analyses

The MPN-SAF TSS50 at week 24 will be analyzed as described below.

- The following will be provided:
    a. The number and percentage of patients in the ITT set for arm 4 evaluable for TSS50 at week 24 (see table below);
    b. The number and percentage of patients in the ITT set for arm 4 non-evaluable for TSS50 at week 24, along with reasons for non-evaluability (see table below).

- The number and percentage of patients achieving a ≥ 50% reduction in TSS at week 24 will be summarized; exact 95% confidence limits of the binomial distribution will be provided. This

rate will be computed over (a) above. Patients will be considered as responders/non-responders based on what follows:

- Patients achieved ≥ 50% reduction from baseline in TSS at week 24: responders.
- Patients did not achieve ≥ 50% reduction from baseline in TSS at week 24: non-responders.
- Patients have TSS = 0/missing at baseline and discontinued (based on the date of end of treatment) before week 19 (Day 127): non-responders.
- Patients have non-missing/non-zero baseline TSS and week 24 TSS is missing per visit window/imputation: non-responders.

- The percent change from baseline to week 24 in the MPN-SAF TSS will be summarized and it will also be presented using a waterfall plot. The waterfall plot will display one bar for each patient included in the analysis and will be sorted in descending order.

- The percent change from baseline to the best post-baseline result in the MPN-SAF TSS will also be summarized.

Note: the changes from baseline as listed above will be computed if both baseline and the post-baseline assessment(s) in the MPN-SAF TSS are available. The summaries will also include the number of not-available data for each assessment under scrutiny (i.e., baseline, post-baseline).

The table below describes the criteria for patients' evaluability/non-evaluability for the MPN-SAF TSS50 at week 24, as well as the possible reasons for non-evaluability.

Criterion	**(Non-)evaluability**	**Rationale for non-evaluability**	**Reason for non-evaluabiltiy**
For patients on treatment at corresponding timepoint of analysis			
Have non-zero/non-missing MPN-SAF TSS at baseline, and have MPN-SAF TSS at week 24.	Evaluable		
Have non-zero/non-missing MPN-SAF TSS at baseline.	Evaluable		
Have MPN-SAF TSS=0 or missing at baseline.	Non-evaluable	(Ongoing at cutoff date with) baseline MPN-SAF TSS = 0 or missing. Percent change from baseline cannot be computed.	Non-evaluable baseline TSS
Have non-zero/non-missing MPN-SAF TSS at baseline, but have no	Non-evaluable	(Ongoing at cutoff date with) no MPN-SAF TSS at week 24 or beyond. Week	Not-available TSS value at week 24

MPN-SAF TSS at week 24 (based on study week) or beyond.		24 TSS may not happen yet or it is not available per visit window or imputation.	
For discontinued patients			
Have non-zero/non-missing MPN-SAF TSS at baseline, and have MPN-SAF TSS at week 24.	Evaluable		
Have non-zero/non-missing MPN-SAF TSS at baseline, and have missing TSS at week 24.	Evaluable		
Have MPN-SAF TSS=0 or missing at baseline and discontinue (based on the date of the end of treatment) before week 19 (Day 127).	Evaluable		
Have MPN-SAF TSS=0 or missing at baseline and discontinue (based on the date of the end of treatment) on/after week 19 (Day 127).	Non-evaluable	Have baseline MPN-SAF TSS = 0/missing and discontinue on/after week 19. Percent change from baseline cannot be computed.	Non-evaluable baseline TSS

Sensitivity Analysis for main analyses

(1) A sensitivity analysis will be conducted on the MPN-SAF TSS50 at week 24 which consists of computing the weekly TSS by applying the following rule: both baseline and post-baseline TSS values will be calculated based on at least 4 non-missing daily total symptom scores for the corresponding week (i.e., baseline, post-baseline). The weekly TSS will be considered as missing if less than 4 daily total symptom scores are available for the week at stake.

The statistical analyses to be conducted are the same as described for the main analysis.

(2) The same analyses as those listed below will be conducted on the PPS analysis set:

- Main analysis,
- Sensitivity analysis (1),
- Supportive and Additional Analysis (see below).

Supportive and Additional Analysis

A set of additional analyses will be conducted on the TSS50 as measured by the MPN-SAF by considering 4 additional post-baseline assessments, namely TSS50 at week 12, week 36, week 48 and week 60. These are defined below. The criteria for patients' (non-)evaluability, as well as the possible reasons for non-evaluability, are specified in Table 10 below.

1. *MPN-SAF TSS50 at week 12*

This is defined as a ≥ 50% decrease from baseline to week 12 in 7-day average TSS as measured by the MPN-SAF.

2. MPN-SAF TSS50 at week 36

This is defined as a ≥ 50% decrease from baseline to week 36 in 7-day average TSS as measured by the MPN-SAF.

3. MPN-SAF TSS50 at week 48

This is defined as a ≥ 50% decrease from baseline to week 48 in 7-day average TSS as measured by the MPN-SAF.

4. MPN-SAF TSS50 at week 60

This is defined as a ≥ 50% decrease from baseline to week 60 in 7-day average TSS as measured by the MPN-SAF.

The MPN-SAF TSS50 at week 12, 36, 48 and 60 will be analysed, separately for each week under scrutiny, as described below.

- The following will be provided:
    a. The number and percentage of patients in the ITT set for arm 4 evaluable for TSS50 at the given week (i.e., 12, 36, 48, 60; see table below for evaluability criteria);
    b. The number and percentage of patients in the ITT set for arm 4 non-evaluable for TSS50 at the given week (i.e., 12, 36, 48, 60), along with reasons for non-evaluability (see table below for details on non-evaluability).

- The number and percentage of patients achieving a ≥50% reduction in the MPN-SAF TSS at the given week (i.e., 12, 36, 48, 60) will be summarized; exact 95% confidence limits of the binomial distribution will be provided. This rate will be computed over (a) above. Patients will be considered as responders/non-responders based on what follows:

    - Patients achieved ≥ 50% reduction from baseline in TSS at the given week (i.e., 12, 36, 48, 60): responders.
    - Patients did not achieve ≥ 50% reduction from baseline in TSS at the given week: non-responders.

- Patients have TSS = 0/missing at baseline and discontinued (based on the date of end of treatment) before:
  - For TSS50 at week 12: week 7 (Day 43): non-responders.
  - For TSS50 at week 36: week 31 (Day 211): non-responders.
  - For TSS50 at week 48: week 43 (Day 295): non-responders.
  - For TSS50 at week 60: week 55 (Day 379): non-responders.

- Patients have non-missing/non-zero baseline TSS and TSS at the given week (i.e., 12, 36, 48, 60) is missing per visit window/imputation: non-responders.

- The percent change from baseline to week 12/36/48/60 in TSS from the MPN-SAF score will be summarized and it will also be presented using a waterfall plot. The waterfall plot will display one bar for each patient included in the analysis and will be sorted in descending order. The percent change from baseline will be computed only when both baseline and the post-baseline assessment are available. The summaries will also include the number of missing data for each time-point under scrutiny (i.e, baseline/post-baseline).

Table 10: Patients' evaluability for MPN-SAF TSS50 at week 12, 36, 48 and 60

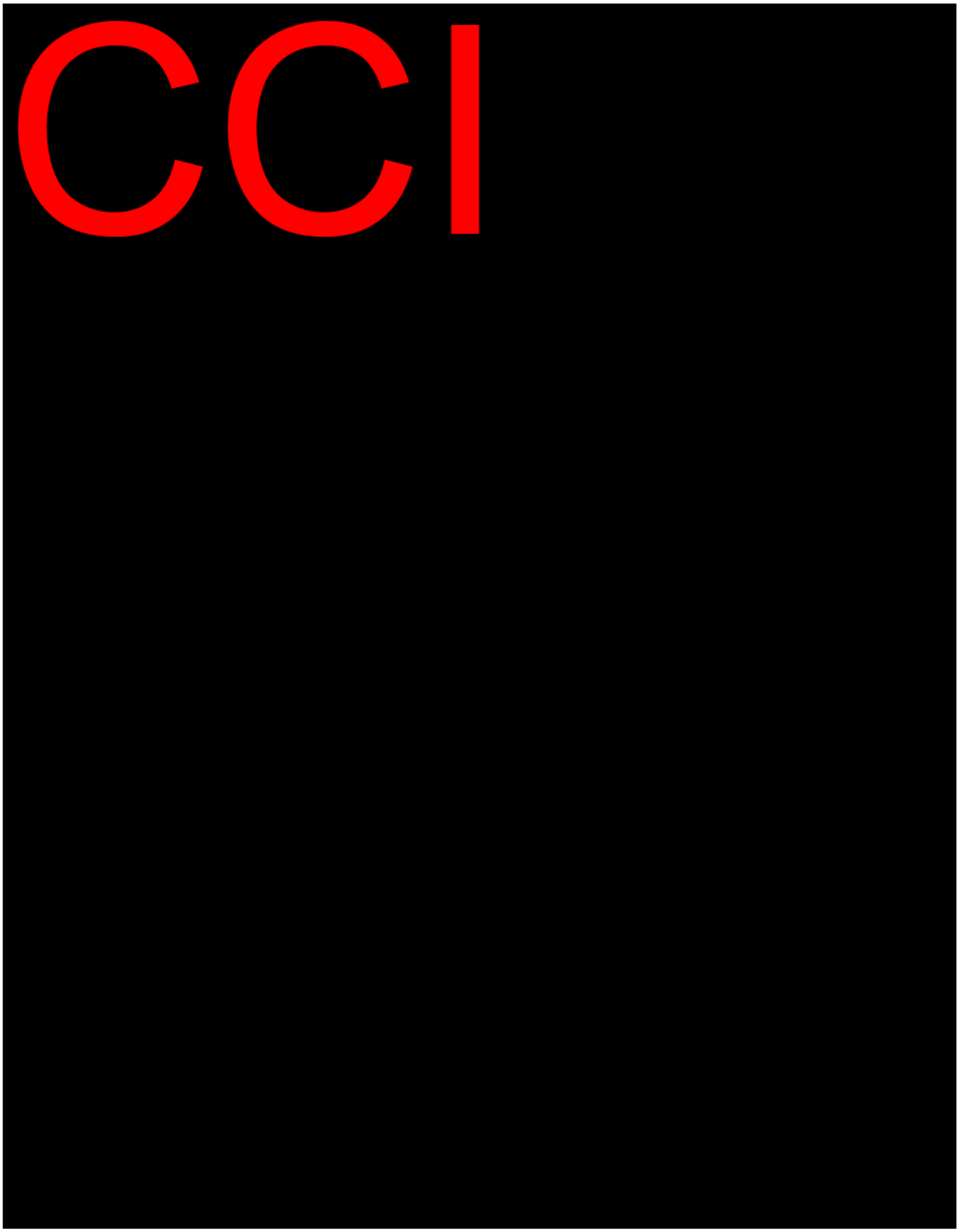
Criterion	(Non-)evaluability	Rationale for non-evaluability	Reasons for non-evaluability
For patients on treatment at corresponding timepoint of analysis			
Have non-zero/non-missing MPN-SAF TSS at baseline, and have MPN-SAF TSS at the given week (i.e., 12, 36, 48, 60).	Evaluable		
Have non-zero/non-missing MPN-SAF TSS at baseline.	Evaluable		
Have MPN-SAF TSS=0 or missing at baseline.	Non-evaluable	(Ongoing at cutoff date with) baseline MPN-SAF TSS = 0 or missing. Percent change from baseline cannot be computed.	Non-evaluable baseline TSS.
Have non-zero/non-missing MPN-SAF TSS at baseline, but have no MPN-SAF TSS (based on study week) at :	Non-evaluable	(Ongoing at cutoff date with) no MPN-SAF TSS at: - Week 7 or beyond (for TSS50 at week 12 only).	Not-available TSS value at week 12/36/48/60*

-For TSS50 at week 12: week 7 (Day 43) or beyond. -For TSS50 at week 36: week 31 (Day 211) or beyond. -For TSS50 at week 48: week 43 (Day 295) or beyond. -For TSS50 at week 60: week 55 (Day 379) or beyond.		- Week 31 or beyond (for TSS50 at week 36 only). - Week 43 or beyond (for TSS50 at week 48 only). - Week 55 or beyond (for TSS50 at week 60 only). TSS for the weeks under scrutiny may not happen yet or it is not available per visit window or imputation.	*<u>*Note*</u>: depending on the week under scrutiny.
For discontinued patients			
Have non-zero/non-missing MPN-SAF TSS at baseline, and have MPN-SAF TSS at the given week (i.e., 12, 36, 48, 60).	Evaluable		
Have non-zero/non-missing MPN-SAF TSS at baseline, and have missing TSS at the given week.	Evaluable		
Have MPN-SAF TSS=0 or missing at baseline and discontinue (based on the date of the end of treatment) before: -For TSS50 at week 12: week 7 (Day 43). -For TSS50 at week 36: week 31 (Day 211). -For TSS50 at week 48: week 43 (Day 295). -For TSS50 at week 60: week 55 (Day 379).	Evaluable		
Have MPN-SAF TSS=0 or missing at baseline and discontinue (based on the date of the end of treatment) on/after: -For TSS50 at week 12: week 7 (Day 43).	Non-evaluable	Have baseline MPN-SAF TSS = 0/missing and discontinue on/after: - Week 7 (for TSS50 at week 12 only). - Week 31 (for TSS50 at week 36 only).	Non-evaluable baseline TSS.

-For TSS50 at week 36: week 31 (Day 211). -For TSS50 at week 48: week 43 (Day 295). -For TSS50 at week 60: week 55 (Day 379).		- Week 43 (for TSS50 at week 48 only). - Week 55 (for TSS50 at week 60 only). Percent change from baseline cannot be computed.	

15.5.7 CCI


CCI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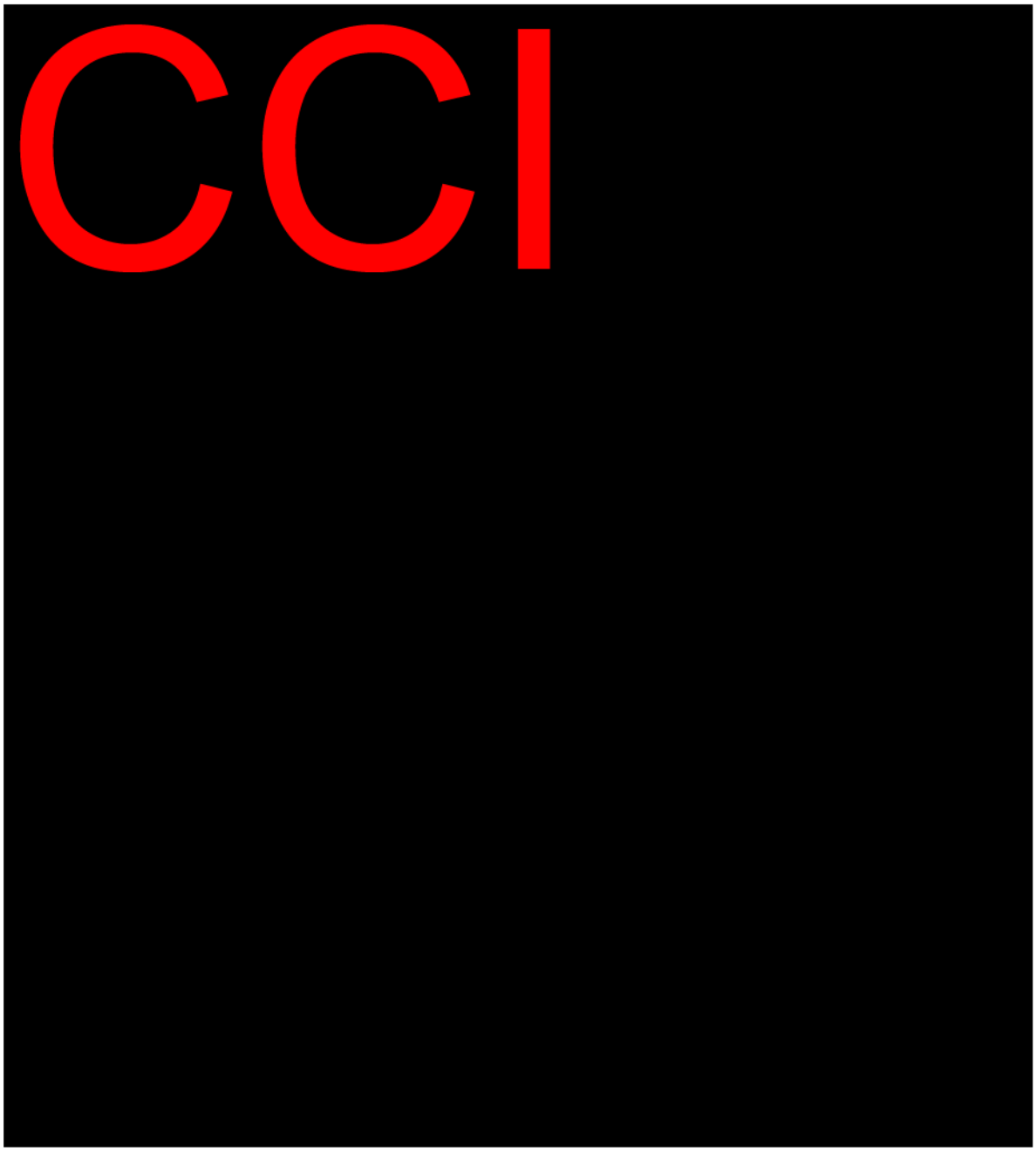

15.5.9 Symptom improvement from the Patient Global Impression of Change (PGIC) at week 24

15.5.9.1 Definition

This is a secondary endpoint for all arms.

The PGIC is a single question to assess the patient's impression of change in their MPN symptoms since the start of study treatment. The patient is asked to evaluate their overall status since the start of the

study by choosing one out the 7 options provided: (1) Very much improved; (2) Much improved; (3) Minimally improved; (4) No change; (5) Minimally worse; (6) Much worse; (7) Very much worse.

PGIC data are recorded in the eCRF page "Patient Global Impression of Change (PGIC)".

See section 23 for the schedule of assessments.

15.5.9.2 **Analysis**

Arm/Cohort: arm 1, arm 2, arm 3, arm 4.

Main analyses

A frequency distribution analysis will be performed for symptom improvement as measured by the PGIC. For the purpose of this analysis, data from the PGIC will be grouped into the following 3 categories:

- Improvement: includes options (1) Very much improved, (2) Much improved, (3) Minimally improved.
- No change: includes option (4) No change.
- Worsening: includes options (5) Minimally worse, (6) Much worse, (7) Very much worse.

- The following will be provided:
  a) The number and percentage of patients in the ITT set for arms 1, 2, 3 and 4 with a PGIC assessment at week 24;
  b) The number and percentage of patients in the ITT set for arms 1, 2, 3 and 4 with missing PGIC per visit window/imputation.

- The number and percentage of patients in each of the categories above will be summarized at week 24 (see section 23 for details on the schedule of events). This will be based on (a) above.

Data will be presented for each arm and overall. For arms 1 and 2, data will be presented by arm and cohort.

See section 22.3 for details on the analysis visit windows, and section 21.1 for imputation rules.

Supportive and Additional Analysis

A set of additional analyses will be conducted on the PGIC by considering the following additional post-baseline assessments: PGIC at week 12, week 36, week 48, week 60, week 72, week 84 and every 12 weeks thereafter.

The same analysis as specified for the main analysis will be conducted. Data will be presented for each arm and overall. Data for arms 1 and 2 will be presented by cohort.

Concordance Analysis

The following two concordance analyses will be conducted.

(1) Concordance rate between PGIC and TSS50 responders/non-responders at week 24

This analysis is aimed at analysing the concordance between the number of responders and non-responders at week 24 in the PGIC versus the TSS50, based on local reads. The concordance rate will be computed both excluding and including missing data. For arms 1, 2 and 3, the TSS50 from the MF-SAF will be used (see section 15.5.1). For arm 4, the TSS50 from the MPN-SAF will be used (see section 15.5.6).

For the purpose of this analysis, patients are classified as PGIC responders/non-responders based on what follows:

- PGIC responders: include options (1) very much improved, (2) much improved; (3) minimally improved.
- PGIC non-responders:
  - Include options (4) No change, (5) Minimally worse, (6) Much worse, (7) Very much worse;
  - PGIC at week 24 is missing per visit window.

The data on the PGIC and the TSS50 will be 1-to-1 matched. Afterwards, the concordance rate will be computed as follows:

		PGIC at week 24			
(MFSAF/MPN-SAF) TSS50 at week 24		Responder	Non-Responder	Missing	Total
	Responder	a	b	c	d
	Non-Responder	e	f	g	h
	Missing	i	j	k	l
	Total	m	n	o	p
		Concordance rate excluding missing data		$100 * \frac{(a+f)}{(a+b+e+f)}$	
		Concordance rate including missing data		$100 * \frac{(a+f+k)}{p}$	

For arms 1, 2 and 3, data will be presented for each arm and overall. Data for arms 1 and 2 will be presented by cohort and overall. Data for arm 4 will be presented separately.

(2) Concordance rate between PGIC and SVR35 responders/non-responders at week 24

This analysis is applicable to arms 1, 2 and 3. The analysis is aimed at evaluating the concordance between the number of responders and non-responders at week 24 in the PGIC versus SVR35. The concordance rate will be computed both excluding and including missing data.

The data on the PGIC and SVR35 will be 1-to-1 matched. Afterwards, the concordance rate will be computed as follows:

		PGIC at week 24			
SVR35 at week 24		Responder	Non-Responder	Missing	Total
	Responder	a	b	c	d
	Non-Responder	e	f	g	h
	Missing	i	j	k	l
	Total	m	n	o	p
		Concordance rate excluding missing data		$100 * \frac{(a+f)}{(a+b+e+f)}$	
		Concordance rate including missing data		$100 * \frac{(a+f+k)}{p}$	

Data will be presented for each arm and overall. For arms 1 and 2, data will be presented by cohort and overall.

Sensitivity Analysis

A sensitivity analysis will be conducted on the PGIC by considering only ePRO records.

The same analysis as specified for the main analysis will be conducted. Data will be presented for each arm and overall. Data for arms 1 and 2 will be presented by cohort.

15.5.10 CCI


CCI


CCI


CCI


CCI


CCI


CCI


CCI


CCI


CCI


CCI

15.8 Overall Survival

15.8.1.1 Definition

Overall Survival (OS) is defined as the period from the date of first administration of study treatment (section 6.1.5.3) until the date of death from any cause, and is computed in months as follows:

OS (months) = [date of death or date of censoring - date of first administration of study treatment+1]/30.4375

The censoring strategy for Overall Survival is described below:

Item	Situation	Date of Censoring	Outcome	Censoring reason reported
1	No event until data cutoff/EOS date	The earlier date out of date of last contact (section 6.1.9) and date of data cutoff/EOS date	Censored	Patient ongoing at data cutoff/EOS date without event
2	Death	Date of death	Event (not censored)	Not applicable
3	Lost to follow up	Date of last contact (section 6.1.9)	Censored	Lost to follow-up

15.8.1.2 **Analysis**

Arm/Cohort: arms 3 .

Main analyses

Overall Survival will be analyzed as follows:

- The number and percentage of patients with event along with causes of death and number of patients with censoring along with reasons for censoring will be summarized.
- The number of patients at risk and the number of patients censored will be summarized.
- The distribution of OS will be estimated using the Kaplan-Meier method, every 6 months and at EOT. The median OS time with 95% confidence intervals will be presented (Brookmeyer and Crowley, 1982). The 25th and 75th percentiles will be estimated as well, along with their 95% CI.
- The follow-up time for OS will be calculated using reverse Kaplan-Meier methodology. Q1, median, Q3 and their 95% CI based on the KM estimates (using Brookmeyer and Crowley 1982 method) will be provided.
- Kaplan-Meier (K-M) method will be presented in tables and displayed graphically.

16 Safety Analysis

The safety endpoints include:

- Adverse events (AEs),
- Deaths,
- Clinical Laboratory tests, vital signs and electrocardiography (ECG),
- ECOG performance status.

Unless otherwise specified, all safety data will be presented for each applicable arm and overall. For Arms 1 and 2, data will be presented by arm and cohort.

16.1 Adverse Events

16.1.1 Dictionary coding of Adverse Events

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be reported by primary system organ class (SOC) and preferred term (PT).

The MedDRA version used for reporting the study will be the version used for coding the trial and will be specified in the clinical study report and as a footnote in the related outputs (if possible).

16.1.2 Grading of Adverse Events

Adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) and the version described in the individual clinical study report. In case of an update of the CTCAE criteria and for legacy studies using an older version of CTCAE some mapping may be necessary when data need to be pooled.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event although there is not necessarily proportionality among grades (a grade 2 is not twice as bad as a grade 1).

If CTCAE grading does not exist for an adverse event, grades 1 – 4 corresponding to the severity of mild, moderate, severe, and life-threatening will be used. CTCAE grade 5 (death) is not used; if an AE results in death then it is documented in the outcome ("fatal").

16.1.3 General rules for AE reporting

AEs will be reported overall for the SAF. Unless otherwise specified, AEs will be tabulated in decreasing frequency by system organ class (SOC) and preferred term (PT).

All summaries of AEs will report the number of patients experiencing the event, and not the number of events. Accordingly, if the same AE is reported more than once for the same patient, this will only appear once.

The following will be summarized:

- TEAEs;
- TEAEs by CTCAE grade by SOC and PT;
- Study Drug-related TEAEs;
- TEAEs by maximum CTCAE grade by PT;
- Grade 3 or higher TEAEs (i.e., as recoded for the field ' NCICTCAE v4.03 Grade' of the eCRF) by SOC and PT;
- Grade 3 or higher study drug-related TEAE (i.e., as recoded for the field ' NCICTCAE v4.03 Grade' of the eCRF) by SOC and PT;
- TEAEs leading to CPI-0610 discontinuation;
- TEAEs leading to ruxolitinib discontinuation;
- Study Drug-related TEAEs Leading to CPI-0610 discontinuation;
- TEAEs resulting in permanent discontinuation from study;
- TEAEs resulting in dose reduction of CPI-0610;
- TEAEs resulting in interruption of CPI-0610;
- Serious TEAEs;
- Serious TEAEs related to CPI-0610;

- Serious TEAEs related to ruxolitinib;
- Most frequent TEAEs (at least ≥ 5 and $\geq 10\%$ incidence) by PT;
- Most frequent TEAEs (at least $> 5\%$ and $\geq 10\%$ incidence) related to CPI-0610 by PT;
- Most frequent TEAEs (at least $> 5\%$ and $\geq 10\%$ incidence) related to ruxolitininb by PT;
- TEAEs leading to death;
- COVID-19 related TEAEs;
- SAEs;
- Serious TEAEs by CTCAE grade by PT;
- SAEs related to CPI-0610;
- SAEs related to ruxolitinib;
- Serious TEAEs resulting in permanent discontinuation of CPI-0610;
- Serious TEAEs resulting in permanent discontinuation of ruxolitinib;
- Serious TEAEs leading to death;
- Serious TEAEs, regardless of study treatment relationship, by primary SOC, PT, and maximum CTCAE grade;
- Serious TEAEs suspected to be related to CPI-0610, by primary SOC, PT, and maximum CTCAE grade.
- Serious TEAEs suspected to be related to ruxolitinib, by primary SOC, PT, and maximum CTCAE grade.
- Most frequent serious TEAEs (at least 2% incidence), regardless of study treatment relationship, by PT and maximum CTCAE grade.
- Most frequent serious TEAEs (at least 2% incidence), suspected to be related to CPI-0610, by PT and maximum CTCAE grade.
- Most frequent serious TEAEs (at least 2% incidence), suspected to be related to ruxolitinib, by PT and maximum CTCAE grade.
- Most frequent non-serious TEAEs, regardless of study treatment relationship by primary SOC, PT, maximum CTCAE grade (at least 5% incidence);
- Non-serious TEAEs;
- TEAEs, regardless of study treatment relationship, by primary SOC, PT, and maximum CTCAE grade;
- Most frequent TEAEs (at least 10% incidence) regardless of study treatment relationship by SOC ,PT and maximum CTCAE grade;
- TEAEs suspected to be related to CPI-0610 by primary SOC, PT, and maximum CTCAE grade;
- TEAEs suspected to be related to ruxolitinib by primary SOC, PT, and maximum CTCAE grade;
- Most frequent TEAEs (at least 10% incidence) suspected to be related to CPI-0610 by SOC, PT, and maximum CTCAE grade;

- Most frequent TEAEs (at least 10% incidence) suspected to be related to ruxolitinib by SOC, PT, and maximum CTCAE grade;
- Grade 3 and 4 TEAEs, regardless of study treatment relationship, by primary SOC, PT and maximum CTCAE grade;
- Grade 3 and 4 TEAEs, suspected to be related to CPI-0610, by primary SOC, PT and maximum CTCAE grade;
- Grade 3, 4 and 5 TEAEs, suspected to be related to ruxolitinib, by primary SOC, PT and maximum CTCAE grade;
- TEAEs leading to study drug discontinuation, regardless of study treatment relationship, by primary SOC, PT and maximum NCI CTCAE grade;
- TEAEs requiring dose adjustment, regardless of study treatment relationship, by primary SOC, PT, and maximum CTCAE grade;
- TEAEs requiring study drug interruption, regardless of study treatment relationship, by primary SOC, PT, and maximum CTCAE grade;
- TEAEs requiring additional therapy, regardless of study treatment relationship, by primary SOC, PT, maximum CTCAE grade;
- AESIs;
- AESIs by CTCAE grade by SOC and PT;
- AEs occurring after CPI-0610 discontinuation up until 30 days*;
- CTCAE Grade 3 or higher AEs occurring after CPI-0610 discontinuation up until 30 days*;
- AEs occurring during interruption of CPI-0610;
- AEs occurring during interruption of ruxolitinib;
- CTCAE Grade 3 or higher AEs occurring during interruption of CPI-0610;
- CTCAE Grade 3 or higher AEs occurring during interruption of ruxolitinib;
- TEAEs leading to CPI-0610 interruption by SOC, PT and NCI CTCAE grade;
- TEAEs leading to ruxolitinib interruption by SOC, PT and NCI CTCAE grade;
- CTCAE Grade 3 or higher TEAEs leading to CPI-0610 interruption by SOC and PT;
- CTCAE Grade 3 or Higher TEAEs leading to ruxolitinib interruption by SOC and PT;
- TEAEs leading to CPI-0610 discontinuation by SOC, PT and NCI CTCAE grade;
- TEAEs leading to ruxolitinib discontinuation by SOC, PT and NCI CTCAE grade;
- CTCAE Grade 3 or higher TEAEs leading to CPI-0610 discontinuation by SOC and PT;
- CTCAE Grade 3 or higher TEAEs leading to ruxolitinib discontinuation by SOC and PT;
- TEAEs leading to CPI-0610 dose reduction by SOC, PT and NCI CTCAE grade;
- TEAEs leading to ruxolitinib dose reduction by SOC, PT and NCI CTCAE grade.

Additionally, an overall summary of AEs will be provided with the number and percentage of patients reporting an event along with the total number of events presented for the following categories:

- All TEAEs;
- All NCI CTCAE grade 3 or higher TEAEs;
- Study drug-related TEAEs;
- Study drug-related NCI CTCAE grade 3 or higher TEAEs;
- All SAEs;
- Study drug-related SAEs;
- Study drug-related NCI CTCAE grade 3 or higher SAEs;
- AESIs;
- TEAEs leading to study drug interruption;
- TEAEs leading to study drug discontinuation;
- TEAEs leading to study discontinuation;
- All deaths (see section 16.2).

Notes:

- Adverse event tables presented by maximum CTCAE grade will provide the following information: (1) maximum individual grade, (2) maximum G3/G4 and (3) Any grade.
- For AEs that occur during interruption of CPI-0610/ruxolitinib, see section 14.3 for definition of dose interruption and section 21.6 for imputation of dose interruption dates.

Furthermore, for Arm 4 only, a summary of thromboembolic events by PT will be generated. SMQs are used to identify thromboembolic events, based on the following document:

- MANIFEST 1 List of SMQ_Embolic and thrombotic events.xlsx.

Finally, separate listings will be generated for what follows:

- AEs;
- CTCAE grade 3 or higher TEAEs ;
- Serious TEAEs;
- Pre-treatment AEs;
- Study drug-related TEAEs;
- CTCAE grade 3 or higher study drug-related TEAEs;
- Study drug-related SAEs;
- TEAEs leading to permanent discontinuation of CPI-0610;
- TEAEs leading to permanent discontinuation of ruxolitinib;
- TEAEs leading to permanent discontinuation from the study;
- TEAEs leading to dose reduction or interruption;
- TEAEs leading to death;
- TEAEs that occurred after discontinuation of CPI-0610*;

- ARDS;
- Accelerated Phase and Transformation to blast phase cases (see section 6.1.18.10 for specifications on the relevant PTs).
- TEAEs.

*Note: AEs/TEAEs that occurred after discontinuation of CPI-0610 are any AEs/TEAE (see definition of TEAEs in section 6.1.18.1) that occurs in the following time interval (including the lower and upper limits): [Date of administration of last dose of study drug (i.e., CPI-0610; section 6.1.5.2) + 30 days], or before the start of alternative (off-study) treatment to MF (i.e., new anti-cancer therapy), whichever occurs first..

16.2 Death

Information on death is captured in the eCRF pages 'Disposition - Mortality Status (DS_2), 'Subject Disposition - End of Treatment (DS)' and 'Subject Disposition - End of Study'.

Death will be summarized for both on-treatment and on-treatment+post-treatment (ALL deaths) periods. On-treatment death is defined as any death that occurred between the first dose of CPI-0610/ruxolitinib until 30 days after the last dose of CPI-0610. Post-treatment death is defined as any death that occurred beyond 30 days after the last dose of CPI-0610.

The following will be summarized:

- Number of deaths by cause of death, separately for on-treatment deaths and ALL deaths;
- COVID-19 related deaths. (On-treatment and ALL deaths).

COVID-19 related deaths are all deaths whose cause of death includes one of the following (not case-dependent): COVID, COVID-10, SARS-CoV-2, Coronavirus.

The tabulation will be based on the SAF. The summaries of ALL deaths will display All deaths, on-treatment deaths and post-treatment deaths as 3 separate categories. A listing for ALL deaths will be generated, with a flag for on-treatment deaths. Additionally, a listing of deaths prior to the first dose of study treatment (i.e., CPI-0610 or ruxolitinib) will be produced on the screened patients population set.

16.3 EudraCT and clinicaltrials.gov requirements for AE and Death summaries

For the legal requirements of clinicaltrials.gov and EudraCT, the following two tables are required:

- Summary of treatment-emergent adverse events which are not serious adverse events with an incidence greater than 5%;
- Treatment-emergent SAEs and SAEs suspected to be related to study treatment.

The summaries above will be provided by SOC and PT on the safety set population.

16.4 Analysis of locally assessed laboratory data, vital signs and ECG

16.4.1 Laboratory Data

Laboratory data are recorded in the corresponding eCRF pages. Unless otherwise specified, the following analysis will be performed for each laboratory parameter as reported in Table 13 below for all scheduled measurements (see section 23 for details on the schedule of events), using the SAF. See section 6.1.17 for baseline definition.

- Descriptive statistics of each laboratory parameter will be summarized, including observed values, absolute and percent change from baseline to each visit. Descriptive statistics will not include Q1 and Q3.
- Listings of all laboratory values (by group of parameters, i.e., hematology, chemistry, etc.) will be provided.
- Listings of all abnormal laboratory values (by group of parameters, i.e., hematology, chemistry, etc.) will be generated.
- Boxplots will be produced for the following sets of parameters by visit:
    - *Hematology parameters:* Lymphocytes (10^9/L), Neutrophils (10^9/L), Platelets (10^9/L), Leukocytes (10^9/L).
    - *Chemistry parameters:* Alkaline Phosphatase (U/L), Alkaline Aminotransferase (U/L), Aspartate Aminotransferase (U/L), Bilirubin (umol/L), Creatinine (umol/L).
    - *Coagulation parameters*: Activated Partial Thromboplastin Time (sec), Prothrombin Time (sec).
- Patient plots of laboratory parameters of interest by visit will be produced. Only patients with ≥ 5x ULN or > 3x baseline value of any parameters of interest will be included in the display. Parameters of interest are: Aspartate Aminotransferase, Alanine Aminotransferase, Alkaline Phosphatase, Total Bilirubin, Creatinine, Albumin and Prothrombin Time.
- An eDISH plot of Maximum Total Bilirubin vs. Maximum Alanine Aminotransferase will be produced. The x-axis will show Maximum Alanine Aminotransferase and will be visualized in logarithmic scale; the y-axis will show Maximum Total Bilirubin.
- An eDISH plot of Maximum Total Bilirubin vs. Maximum Aspartate Aminotransferase will be produced. The x-axis will show Maximum Aspartate Aminotransferase and will be visualized in logarithmic scale; the y-axis will show Maximum Total Bilirubin.
- A shift table for anemia will be produced at each visit, presenting the number and percentage of patients in each bivariate category (i.e., baseline vs. each post-baseline assessment) with CTCAE v4.0 grades for anemia 1, 2 and 3 (see Table 14 below for definitions of CTCAE v4.0 grades for anemia).
- A shift table for thrombocytopenia will be produced at each visit, presenting the number and percentage of patients in each bivariate category (i.e., baseline, post-baseline assessment) with CTCAE v4.0 grades for thrombocytopenia 1, 2, 3 and 4 (see Table 14 below for definitions of CTCAE v4.0 grades for thrombocytopenia).
- Listing of urine/serum β-hCG pregnancy test.

- Shift tables for serum lipid panel including total cholesterol, cholesterol low density lipoprotein (LDL), cholesterol high density lipoprotein (HDL), triglycerides will be produced at each visit, presenting the number and percentage of patients in each bivariate category (i.e., baseline, post-baseline assessment) with respect to the clinical categories indicated in Table 15 below, depending on parameter [5].
- Shift tables from baseline to worst post-baseline will be produced for selected laboratory abnormalities, presenting the number and percentage of patients in each bivariate category (i.e., baseline, worst post-baseline) with CTCAE v4.03 grades 1-to-4, as applicable depending on the laboratory abnormality. The set of laboratory abnormalities under scrutiny is displayed in Table 15. 1 below and is indicated under the CTCAE Term. Table 15. 1 also provides the definitions of the CTCAE grades for each of the selected abnormalities, together with the laboratory parameter involved for the derivation. Based on CTCAE grades definitions, the worst post-baseline assessement is the assessment with the highest CTCAE grade. If a patient has only one post-baseline assessment for a given parameter/abnormality, this will be considered for the worst post-baseline assessment.

Table 13: Laboratory Parameters

	Parameter (SI unit)
Coagulation	• PT (sec) • aPTT (sec) • INR
Haematology	• RBC (10^12/L) • Hgb (g/dL) • Hematocrit (L/L) • Platelet count (10^9/L) • Total WBC count (10^9/L) • Neutrophils (10^9/L)* • Eosinophils (10^9/L)* • Basophils (10^9/L)* • Lymphocytes (10^9/L)* • Monocytes (10^9/L)* • Blast cells (10^9/L) • Nucleated Erythrocytes (10^12/L) • Bands/Stabs • Myelocytes (10^9/L) • Metamyelocytes (10^9/L) • Promyelocytes (10^9/L)
Clinical Chemistry	• Sodium (mmol/L) • Potassium (mmol/L) • Total Carbon Dioxide (mmol/L) • Chloride (mmol/L) • Serum Glucose (mmol/L) • BUN (mmol/L) • Serum Creatinine (µmol/L) • Total Bilirubin (µmol/L) • Direct Bilirubin (µmol/L) • Alkaline Phosphatase • AST (SGOT) (IU/L) • ALT (SGPT) (IU/L) • LDH (IU/L)

	• Uric Acid (mmol/L) • Calcium (mmol/24h) • Phosphorus (mmol/L) • EPO (IU/L) • CRP • Iron (µmol/L) • Iron Binding Capacity (µmol/L) • Ferritin (µg/L) • Transferrin Saturation (%)
Serum Lipids	• Total Cholesterol (mmol/L) • Cholesterol LDL (mmol/L) • Cholesterol HDL (mmol/L) • Triglycerides (mmol/L)
Bone marrow biopsy	• Blast Cells (%)

ALT (SGPT) = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST (SGOT) = aspartate aminotransferase; BUN = blood urea nitrogen; CRP = C-reactive protein; EPO = erythropoietin; HDL = high density lipoprotein; Hgb = hemoglobin; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low density lipoprotein; PT = prothrombin time; RBC = red blood cell; WBC = white blood cell.

*For patients with missing neutrophils (10^9/L), eosinophils (10^9/L), basophils (10^9/L), lymphocytes (10^9/L) and monocytes (10^9/L), the parameter absolute count will be derived based on the following formula:

Parameter (10^9/L) = Parameter/Leukocytes (%) * Leukocytes (10^9/L)

Table 14: Definitions of CTCAE v4.0 Grades for Anemia and Thrombocytopenia

	Anemia	**Thrombocytopenia**
CTCAE v4.0 Grade		
Grade 1	Hgb: • < LLN - 10.0 g/dL; • < LLN -6.2 mmol/L; • < LLN - 100 g/L.	Platelet count: • < LLN -75,000/mm3; • < LLN-75.0 x 10^9/L
Grade 2	Hgb: • < 10.0 - 8.0 g/dL; • < 6.2 - 4.9 mmol/L; • < 100 -80 g/L.	Platelet count: • < 75,000 - 50,000/mm3; • < 75.0 - 50.0 x 10^9/L
Grade 3	Hgb: • < 8.0 g/dL; • < 4.9 mmol/L; • < 80 g/L;	Platelet count: • < 50,000 - 25,000/mm3; • < 50.0 - 25.0 x 10^9/L
Grade 4	-	Platelet count: • < 25,000/mm3; • < 25.0 x 10^9/L

LLN= lower limit of the normal laboratory range.

Table 15: Definitions of Clinical Categories for Serum Lipid Panel Parameters

Parameter	Clinical Category*
Total Cholesterol	• Desirable: < 5.17 mmol/L • Borderline high: 5.17 - 6.18 mmol/L • High: ≥ 6.18 mmol/L
Low Density Lipoprotein (LDL) Cholesterol	• Optimal: < 2.59 mmol/L • Near or above normal: 2.59-3.34 mmol/L • Borderline high: 3.36 - 4.11 mmol/L • High: 4.13 - 4.88 mmol/L • Very High: ≥ 4.91 mmol/L
High Density Lipoprotein (HDL) Cholesterol	• Low: < 1.03 mmol/L • High: ≥ 1.55 mmol/L
Triglycerides	• Normal: < 1.8 mmol/L • High: ≥ 1.8 mmol/L

*Note: reference ranges are expressed in SI units.

Note: for Hgb, g/dL will be derived from the SI unit for Hgb (i.e., g/L). To obtain g/dL, divide the value in g/L by 10.

Table 15. 1: Selected Laboratory Abnormalities and CTCAE v4.03 Grades Definitions

		CTCAE v4.03 Grade			
Parameter	**CTCAE Term**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Alanine Aminotransferase	Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Alkaline Phosphatase	Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Aspartate Aminotransferase	Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
(Total) Bilirubin	Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
(Ionized) Calcium	Hypocalcemia	<LLN - 1.0 mmol/L	<1.0 - 0.9 mmol/L	<0.9 - 0.8 mmol/L	<0.8 mmol/L
	Hypercalcemia	>ULN - 1.5 mmol/L	>1.5 - 1.6 mmol/L	>1.6 - 1.8 mmol/L	>1.8 mmol/L
Creatinine	Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN

(Serum) Glucose	Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L;
	Hyperglycemia	>ULN - 160 mg/dL; >ULN - 8.9 mmol/L	>160 - 250 mg/dL; >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L;	>500 mg/dL; >27.8 mmol/L;
Potassium	Hypokalemia	<LLN - 3.0 mmol/L	-	<3.0 - 2.5 mmol/L;	<2.5 mmol/L;
	Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L;	>7.0 mmol/L;
Sodium	Hyponatremia	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L;
	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L;	>160 mmol/L;
Activated partial thromboplastin time	Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage	-
Hemoglobin	Anemia	See Anemia, in Table 14 of SAP v4.0, section 16.4.1			
	Hemoglobin increased	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	-
Leukocytes	White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10^9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10^9 /L	<1000/mm3; <1.0 x 10^9 /L
Lymphocytes	Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10^9/L	<800 - 500/mm3; <0.8 - 0.5 x 10^9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10^9 /L	<200/mm3; <0.2 x 10^9 /L
Neutrophils	Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10^9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10^9 /L	<500/mm3; <0.5 x 10^9 /L
Platelets	Platelet count decreased (Thrombocytopenia)	See Thrombocytopenia, in Table 14 of SAP v4.0, section 16.4.1			
Cholesterol	Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L
Triglycerides	Hypertriglyceridemia	150 - 300 mg/dL; 1.71 - 3.42 mmol/L	>300 - 500 mg/dL; >3.42 - 5.7 mmol/L	>500 - 1000 mg/dL; >5.7 - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L;

LLN= lower limit of the normal laboratory range; ULN= upper limit of the normal laboratory range.

Notes to Table 15. 1:

- For the CTCAE grades classification of baseline values: if the grade definition provides a condition based on baseline, this is not applicable to the grade assignment for the parameter at baseline and the alternative condition will be used. For example, for creatinine increase, the following conditions are provided for Grade 1 assignment: (a) >1 - 1.5 x baseline; (b) >ULN - 1.5 x ULN. In such a case, condition (b) will be used to assign a CTCAE grade to the baseline value.

- If more than one condition is available for the assignment of the CTCAE grade, assign the CTCAE grade as resulting from the condition that generates the most severe result.

- Should a conversion unit for Hgb be necessary, refer to the corresponding specification above to convert Hgb in SI unit (i.e., g/dL).

- If, throughout the study, a patient has more than one post-baseline assessment for the same parameter that falls within the same CTCAE grade and if the grade at stake represents the worst post-baseline, the earliest of these assessments will be used for the purpose of the analysis. For example, if a patient has 3 post-baseline assessments for cholesterol dated, respectively, 20 November 2022, 20 December 2022 and 21 January 2023, and all of these assessments fall within a grade 4 cholesterol high based on absolute values of cholesterol, the assessment dated 20 November 2022 will be considered as the worst post-baseline for the corresponding shift table of cholesterol high.

- For the baseline and/or post-baseline assessments whose values for the parameter under scrutiny do not fall within the ranges for any of the CTCAE grades categorization, they will be assigned Grade 0.

16.4.2 Vital signs

Vital signs are recorded in the Vital Signs pages of the eCRF. Vital signs parameters include: temperature, pulse (beats/min), respiratory rate (breaths/min), systolic blood pressure (mmHg), diastolic blood pressure (mmHg) and weight. The following analysis will be performed for each parameter for all scheduled measurements (see section 23 for details on the schedule of events), using the SAF. See section 6.1.17 for baseline definition.

- Descriptive statistics of each vital signs parameter will be summarized, including observed values and absolute and percent changes from baseline to each visit. Boxplots will also be produced.
- Listings of all vital signs parameters will be provided as well.

Body temperature will be reported in Celsius, weight in Kilograms.

16.4.3 ECG

ECG analysis is based on the SAF. For each scheduled assessments, ECG data are recorded in the eCRF ECG page. ECG parameters include: RR interval (msec), PR Interval (msec), QT Interval (msec), QTcB (msec), QTcF (msec), QRS interval (msec), and the result of ECG (i.e., Normal, Abnormal Not Clinically Significant (NCS), Abnormal Clinically Significant (CS)).

- Descriptive statistics of each continuous parameter will be summarized by visit, including observed values and change from baseline to each visit.

- A shift table will be produced at each visit, presenting the number and percentage of patients in each bivariate category (i.e., baseline vs. each post-baseline assessment) with regards to the result of ECG (Normal, Abnormal NCS, Abnormal CS).

- For QTcF interval: the number and percentage of patients within each of the categories below will be displayed by visit.

    - Increase from baseline to each visit in QTcF interval:
    - > 30 msec and ≤ 60 msec
    - > 60 msec

- The number and percentage of patients with QTcF interval > 500 msec will be presented at each visit.
- For PR interval: the number and percentage of patients within each of the categories below will be presented by visit.
    - Increase from baseline to each visit in the PR interval:
        - > 25% and to > 200 msec
        - ≤ 10 msec, > 10 msec but ≤ 20 msec, and > 20 msec
        - ≤ 25 msec, > 25 msec but ≤ 50 msec, and > 50 msec
- For QRS interval: the number and percentage of patients with QRS interval increase from baseline to each visit in QRS interval > 25% and to > 110 msec will be tabulated by visit.

If not available in the eCRF, QT interval corrected by Bazett's formula (QTcB) and by Fridericia's formula (QTcF) will be derived as follows:

- QTcB = QT/(RR)^1/2
- QTcF = QT/(RR)^1/3

RR will be derived as follows:

- RR (sec) = 60/HR

And multiplied by 1000 to obtain RR in msec.

Note: HR is collected under the "ventricular rate (beats/min)" label. This will be considered as HR.

The same analyses as above will also be provided by gender (male/female). A listing of ECG parameters will also be produced.

16.5 ECOG performance status

ECOG performance status, as collected in the ECOG Performance Status eCRF page, will be analysed on all patients in the SAF with one baseline and at least one post-baseline assessment for ECOG performance status.

The following will be provided:

- A summary of ECOG performance status will be produced, including the number and percentage of patients in each category by visit.
- A shift table from baseline to worst post-baseline result will be produced, presenting the number and percentage of patients in each bivariate category (i.e., baseline, worst post-baseline) with regards to the result of the ECOG performance status (i.e., 0-to-4).

16.6 Physical examination

Complete physical examination at screening includes height, weight, clinical signs and symptoms, and palpable spleen length. The complete physical exam includes assessment of splenomegaly. Subsequent physical exams (within 72 hours prior to the start of Cycle 2, 3 and then every odd numbered cycle and at the EOT visit) may be targeted to areas of known disease and potential areas of MF/MPN involvement. Targeted physical examination must include weight and examination of the abdomen to assess the spleen length by palpation.

See schedule of assessments in section 23 for full details on physical examination assessments.

Data on physical examination are collected in the following eCRF pages:

- "Hepatic and Splenic Measurements by Palpation (HS)" and "Hepatic and Splenic Measurements History (HSH)": for data on hepatic and splenic measurement by palpation before C1D1;

- "Physical Examination (PE)";

- "Physical Examination Post Baseline (PE_1)".

Data on physical examination will be listed.

17 Pharmacodynamic Analysis

17.1 Specifications for Pharmacodynamics Analysis

Pharmacodynamic endpoints include IL-8 (CXCL8) gene expression in peripheral blood, as well as plasma cytokine levels and blood mutation profiling before and after treatment (ratio of mutant to wild type MF-relevant alleles).

<u>For IL-8 (CXCL8) gene expression in peripheral blood:</u>

A peripheral blood sample for IL-8 gene expression is collected prior to CPI-0610 dosing as well as at 4 hours after CPI-0610 dosing on: C1D1, C1D14, C3D1 and, afterwards, on D1 of any cycle where the dose of CPI-0610 is changed - see section 23 for details on the schedule of events.

Ct-IL-8 is normalized to the mean of the housekeeping genes Ct-B2M and Ct-PPIB. On each respective visit, IL-8 changes from pre- to 4 hours post dosing of CPI-0610 are analysed. Further analysis

specifications for the derivation of the ratio obtained from Ct-IL-8, Ct-B2M and Ct-PPIB are provided in section 25.

For Plasma Cytokine Levels and Blood Mutation Profiling:

A peripheral blood sample for measurement of plasma cytokine levels is collected prior to CPI-0610 dosing on C1D1, anytime on C1D14, Day 1 of cycles 3, 5, 7 and 9 and at EOT visit - see section 23 for details on the schedule of events.

A peripheral blood sample for the assessment of mutated allele burden is collected prior to CPI-0610 dosing on C1D1, after 24 weeks of treatment (C9D1) and every 24 weeks (i.e., 8 cycles) thereafter (suspended with protocol amendment 12, version 13), and at EOT visit - see section 23 for details on the schedule of events.

For Blood Mutation Profiling, blood allelic burden for selected genes are used for the statistical analysis as described below. The following selected genes are considered:

- JAK2-V617F
- CALR
- MPL
- ASXL1
- HMR (*ASXL1, EZH2, IDH1/2, SRSF2, U2AF1)*
- Triple negative

Further analysis specifications for blood mutation profiling data are provided in section 25.

Baseline for plasma cytokine levels and blood mutation profiling is the latest non-missing assessment in peripheral blood collected on or before C1D1 and on or after ICF signature date.

Missing values for pharmacodynamic data will not be imputed.

17.2 Statistical Analysis

Pharmacodynamic data will be analysed as described below.

Unless otherwise specified, all pharmacodynamic data will be presented for each applicable arm and overall. For Arms 1 and 2, data will be presented by arm and cohort.

The following will be provided:

- For C1D1, C1D14, C3D1, percent changes from pre-dose to 4 hours post-dosing of IL8 (CXCL8) gene expression in peripheral blood will be summarized and presented graphically using a boxplot.

Finally, the following listings will be generated:

- Mutation Profiles: this listing will report individual patients' data on the following selection of blood allelic burden genes: JAK2-V617F, CALR, MPL, ASXL1, HMR (*ASXL1, EZH2, IDH1/2, SRSF2, U2AF1),* Triple Negative*;*

- Cytokine Profiles: this listing will report individual patients' data on plasma cytokine levels and will include absolute and percent change from baseline;
- IL-8 Gene Expression;
- Bone Marrow Fibrosis central reads.

18 Pharmacokinetic Analysis

Plasma concentration data of CPI-0610 and/or ruxolitinib will be summarized for all patients who receive at least 1 dose of study drug and who have at least 1 quantifiable concentration, regardless of their inclusion in the PK population. PK concentration values will be listed for each individual by study drug, treatment arm, cycle, day, and dose, and the following descriptive statistics for will be provided: N (number of patients with non-missing data), Mean (arithmetic mean), standard deviation (SD), arithmetic percent coefficient of variation (CV%) minimum, median, and maximum.

PK parameters for plasma CPI-0610 and ruxolitinib will include, but are not limited to, C_{max}, t_{max}, C_{trough}, AUC_{last}, $AUC_{0\text{-}8,ss}$, $C_{max,ss}$, and $t_{max,ss}$. All patients in the PK population will be included in the descriptive statistics for the PK parameters. PK parameter values will be listed for each individual by study drug, treatment arm, cycle, day, and dose, and the following descriptive statistics will be provided: N, Mean, SD, CV%, median, minimum, and maximum. Geometric mean and geometric percent coefficient of variation (Geometric CV%) will be calculated for continuous PK parameters. T_{max} will be presented as median, minimum, and maximum.

CCI [redacted]

19 General guidance on reporting

19.1 Document headers, footers and layout

The following table specifies general information of headers, footers and layout.

Orientation	Landscape
Paper Size	A4
Margins	Top: 2 cm Bottom: 2 cm Left: 2 cm Right: 2 cm Header: 1.27 cm Footer: 1.27cm
Font	Courier New 8pt
Headers	Constellation Pharmaceuticals, Inc. /Protocol: Protocol number (Left); Page X of Y (Right) TLF Number and Title
Footers	SAS program name Source Data Extract date Date,/Time of TLF generation Database <CUTOFF/ LOCK> date: <YYYY-MM-DD>

The font size may be reduced as necessary to allow additional columns to be presented, but not at the expense of clarity. Also the orientation may be changed to portrait if appropriate.

All other table-unique footers should be presented above the aforementioned footers, as the following display:

- footnote 1
- footnote 2
- footnote 3

SAS program name -- source data -- extract date -- date/time of TLF generation

In the applicable outputs, the MedDRA version and WHO-DDE version used for reporting the study will be specified as a footnote.

- MedDRA Version <xx.x> has been used for the reporting

- WHO-DDE Version <xx.x> has been used for the reporting

At the end of the trial all MedDRA and WHO DDE codes will be updated to the newest versions.

19.2 Presentation of output numbering and titles within this document

In practice, the numbering and title for all tables, figures and listing will be formatted as follows, respectively:

Table/ Figure 14.x.x.x

Title Title Title Title Title Title

Population

Listing 16.x.x.x

Title Title Title Title Title Title

Population

19.3 General rules for presenting tables and listings

Data as documented in the eCRF will be listed and/or tabulated using descriptive statistics or counts/percentages depending on the nature of data.

The following general rules for presenting listings should be applied by default for all listings.

Unless differently mentioned, all listings should contain the following information: "Patient identifier" and "Site ID". For data collected on visit level, the visit should be placed in the third column. The default sorting order is by patient number and event/assessment date unless otherwise stated.

Where a listing or table has been planned, but no data meet the criteria, then a single line will be provided in the output, explaining that no data meeting the criteria is present.

In all listings for Arm 4 only, the Arm/Cohort column will not be showed, " - Arm 4" will appear in the title.

For all laboratory parameters, SI units are used as default.

When a variable collected in the eCRF is linked to another variable, one or both variables may be presented in the same column of the listing or in adjacent columns if space permits this.

For example:

- 'Setting'='OTHER' and 'Other, specify'='Lung'
  "OTHER: Lung" will be displayed in the column as 'Setting'.
- 'Dose'='120' and Dose unit ='mg'
  '120 mg' will be displayed in the column as 'dose (unit)'.
- If Date = "2012-05-12" and Study day ="5", then "12MAY2012 / 5" will be displayed in the column as 'Date / Study Day'.
- If End date = " " and ongoing is ticked, then "Ongoing" will be displayed in the column as 'End date / Study Day'.

19.4 Presentation of analysis sets

The outputs to be produced based on this document will use 'ITT', 'SAF', 'PPS' and 'PDAS' in the table/figure/listing titles.

19.5 General rules for presenting frequencies and percentages

If a summary table displays only categorical variables then the convention illustrated in the following example will be used:

Preferred Term	**Arm A** **N=xx** **n (%)**	**Arm B** **N=xx** **n (%)**	**Overall** **N=xx** **n (%)**
Total	xx (xx.x)	xx (xx.x)	xx (xx.x)
Fatigue	xx (xx.x)	xx (xx.x)	xx (xx.x)
Nausea	xx (xx.x)	xx (xx.x)	xx (xx.x)
Anemia	xx (xx.x)	xx (xx.x)	xx (xx.x)

However, if a summary table displays both continuous and categorical variables then the convention illustrated in the following example will be used:

	Arm A **N=xx**	**Arm B** **N=xx**	**Overall** **N=xx**
Sex, n (%)			
Male	xx (xx.x)	xx (xx.x)	xx (xx.x)
Female	xx (xx.x)	xx (xx.x)	xx (xx.x)
Age (Years)			
n	xx	xx	xx
Mean	xx.xx	xx.xx	xx.xx
StD	xx.xxx	xx.xxx	xx.xxx
Median	xx.xx	xx.xx	xx.xx
25th quartile	xx.xx	xx.xx	xx.xx
…75th quartile	xx.xx	xx.xx	xx.xx
Minimum	xx.x	xx.x	xx.x
Maximum	xx.x	xx.x	xx.x

When applicable, continuous variables are presented in the table with the following number of decimal places: n with 0 decimal places; mean and 95% CLs of mean, median and 95% CLs of median, Q1 and Q3 with 1 more decimal place than as collected (or clinically meaningful); standard deviation and standard error with 2 more decimal places than as collected (or clinically meaningful); minimum and maximum with the same decimal places as collected (or clinically meaningful). Note that "collected" refers to the source data of the variable of interest or the input data.

Percentages for dichotomous/categorical variables are presented in the tables with 1 decimal place, excluding 0 and 100, and in brackets, without empty spaces between the brackets and the percentage value.
P-values are displayed with 4 decimals, and if they are less than 0.0001, are presented as < .0001.

19.6 **Presentation of dates**

Calendar dates and times (optional) in all the listings will be displayed in the format:

DDMONYYYY hh:mm e.g. 15JAN2019 08:20.

Note: If time is not collected, calendar dates will be displayed as: DDMONYYYY.

20 References

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

[2] Clopper, C. J., & Pearson, E. S. (1934). The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. *Biometrika*, *26*(4), 404–413.

[3] Barosi G, Birgegard G, Finazzi G, et al. Response criteria for essential thrombocythemia and polycythemia vera: result of a European LeukemiaNet consensus conference. Blood. 2009; 113(20): 4829-4833.

[4] Cervantes F., Dupriez B., Pereira A., et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. Blood 2009; 113(13): 2895-2901.

[5] Kratz A., Ferraro M., Sluss P.M., et al. Laboratory Reference Values. *The New England Journal of Medicine*, 2004; 351: 1548-1563.

21 Appendix: Handling of Missing Data

21.1 Handling of Missing Efficacy data

Imputation rules for missing spleen volume value at an analysis visit

After the analysis visit window rules have been applied (section 22.1), impute missing spleen volume value for any visit as follows:

1. If any visit window has missing value for spleen volume, the missing value will be imputed using the next available numerical record up to day 630 (Week 90). Records after day 630 will not be used for the imputation.
2. If any visit window has missing value for spleen volume and there are no more recorded values afterwards, then no imputation will be performed and the value is considered as missing.

Imputation rules for missing total symptom score (TSS) at an analysis visit

No further imputation will be applied for missing values of TSS from the MFSAF v4.0 or the MPN-SAF after the application of the study week definition and visit window rules (sections 22.2 and 22.3, respectively).

Imputation rules for missing PGIC at an analysis visit

No further imputation will be applied for missing values of the PGIC after the application of the visit window rules (section 22.3).

Imputation rules for missing early anemic response and anemic response at an analysis visit

No further imputation will be applied for missing values of early anemic response data and anemic response data after the application of the visit windows rules (section 22.4).

Imputation rules for missing bone marrow fibrosis grade

No further imputation will be applied for missing values of bone marrow fibrosis grade data after the application of the visit windows rules (section 22.5).

Imputation rules for missing IWG-MRT response categories

No further imputation will be applied for missing values of IWG-MRT response categories data after the application of the visit windows rules (section 22.7)

21.2 Handling of Missing or incomplete End of Treatment/End of Study date

EOS date:

If EOS date is missing, then the data cutoff date will be used for ongoing subjects; in all other cases, the date of last contact will be used.

If EOS date < date of last contact, the date of last contact will be used.

EOT date:

If EOT date is missing, then the date of last administration of study drug will be used.

If EOT date is partial:

- Day and/or month are missing: replaced with the lower limit. If the imputed EOT date < date of last administration of study drug, then EOT date = date of last administration of study drug.

21,3 Handling of Missing Dates/Months/Years for Adverse Events

The following rules are applied for handling of missing or partial dates for AE:

Type of date	Date is incomplete	Date is missing
AE onset	- If the end date of the AE is after the start of treatment (i.e., date of first administration of study treatment - section 6.1.5.3), and if the start of treatment falls within the range of possible dates, then the date of start of treatment (i.e., date of first administration of study treatment) is used. - In all other cases, the lower limit is used.	- The earliest between date of AE resolution and date of start of treatment (i.e., date of first administration of study treatment - section 6.1.5.3) is used.
AE resolution	- Day is missing: Replaced by the upper limit. - Day and month are missing: replaced by the upper limits.	No replacement, and the AE is considered as ongoing.

21,4 Handling of Missing Dates/Months/Years for Prior/Concomitant Medication and Prior Therapy

The following rules are applied for missing/partial dates of prior and concomitant medications and of prior therapies:

Type of date	Date is incomplete	Date is missing
Start date of medication/therapy	- Lower limit except when: The end date of the medication/therapy is not collected or with upper limit after the start of treatment (i.e., date of first administration of study treatment - section 6.1.5.3) AND the day of start of treatment falls within the range of possible dates. In which case, the date of start of treatment is used.	- Replaced by the date of the ICF signature, except if the end date of the medication/therapy is before ICF signature date. In which case, the end date of the medication/therapy is used.

End date of medication/therapy	- Upper limit except when: The start date of the medication/therapy is before the start of treatment (i.e., date of first administration of study treatment - section 6.1.5.3) or missing AND the date of start of treatment falls within the range of possible dates. In which case, the date of start of treatment is used.	No replacement, and the medication/therapy is considered as ongoing.

21.5 Handling of Missing/incomplete dates for data other than Adverse Events or prior/concomitant medications or prior therapies

This section describes some general principles to be followed in the case of missing or incomplete dates other than adverse events or prior/concomitant medications. The dates that are missing or incomplete are derived as follows:

- Dates are split in 3 parts: year, month and day. Year is the top-level, month is medium level and day is low level.
- If a part is missing, all other parts of a lower level are considered to be missing. This means that a DDMMMYYYY date '21---2021' is considered as '-----2021'.

Missing parts for specific dates are changed into acceptable non-missing values as described in Table 16. In the following, 'lower limit' and 'upper limit' refer to the minimum or maximum, respectively, of a possible date. For example, if the day is missing, the lower limit is the first day of the given month and the upper limit is the last day of the given month. If the day and month are missing, the lower limit refers to the first day of the given year and the upper limit to the last day of the given year. In case more than one date is missing per patient, imputation will be performed following the order specified in Table 16.

Table 16: Handling of missing and incomplete dates

Type of date	Date is incomplete	Date is missing
Records of medical history - start date	- Day is missing: Replaced by the lower limit. - Day and month are missing: no replacement.	No replacement
Records of medical history - stop date	- Day is missing: Replaced by the lower limit. - Day and month are missing: no replacement.	No replacement

	Note: if imputed stop date < start date, then stop date = start date.	
Date of measurements: Laboratory assessments, Vital signs, ECG.	- Day is missing: Replaced by the lower limit. - Day and month are missing: no replacement.	No replacement
Date of procedure: transfusion	- Day is missing: Replaced by the lower limit. - Day and month are missing: no replacement.	No replacement
Death date	Use the latest date among: - Lower limit - Any date record as collected in the eCRF	- Use the latest date among any date record as collected in the eCRF
Date of birth	- Day is missing: replaced by the lower limit; - Day and month are missing: 1st January will be imputed.	No replacement.

21.5.1 Handling of Missing/incomplete dates for date of initial MF/ET diagnosis

The table below reports the rules to apply for partial dates of initial MF/ET diagnosis.

Day	Month	Year	Treatment start	Imputation rule
Missing	Non-missing	Non-missing	Month and year for start of treatment ≥ month and year of initial MF diagnosis	Replace missing day with 1st of initial diagnosis month.
Missing	Missing	Non-missing	Year of start of treatment ≥ year of initial MF diagnosis	Replace missing day and month with 1st Jan of initial diagnosis year

In all other cases, no imputation will be performed.

21.6 Handling of Missing dates for dose interruption data

The date of CPI-0610/ruxolitinib dose interruption will be derived by adopting an approach based on the date of the last available intake and the planned day of the cycle in which the dose is interrupted, and it will be computed as date of last available dose + n. of days between the last available intake and the skipped intake. For example, if a dose is interrupted at day 2 of a given cycle, the date for this interruption will be computed as date of day 1 of the cycle + 1. If interruptions occur, for example, from day 10 to day 21 of a given cycle, the dates for these interruptions will be computed as date of day 9 + 1 (for day 10), date of day 9 + 2 (for day 11), and so on.

In addition to what above, the following rules apply:

- If the dose interruption occurs at C1D1, then the date of C1D1 visit will be used.
- If the dose interruption occurs at C2D1, and the date of C2D1 visit is not missing, then the date of C2D1 visit will be used.
- For ruxolitinib: if, for the same day, a PM dose is skipped and the AM dose is done, then the date of the AM dose will be used as date of the skipped PM dose.

22 Appendix: Visit Windows

22.1 Visit Windows for Spleen Volume Response (SVR)

Table 17 below illustrates the visit windows and the target study day for splenic volume data that are analyzed by visit.

Table 17: Analysis visit window definition for spleen volume response

Visit*	Target Study Day per Protocol	Analysis Visit Window (in days)	
		Lower Bound	Upper Bound
Baseline	Last non-missing before C1D1	NA	Day -1 (the day prior to Day 1)
Week 12	Day 84	Day 43 (6*7+1)	Day 126 (18*7)
Week 24	Day 168	Day 127 (18*7+1)	Day 210 (30*7)
Week 12*k (k=3, 4, 5, …)	7*12*k	Day [(12*k-6)*7+1]	Day [(12*k+6)*7]

* Visit name for analysis purpose is used to report data in tables, figures and listings.

SVR data collected on all scheduled or unscheduled visits, including the end of treatment/end of study assessments, will be mapped to an appropriate analysis visit window using the following rules:

1. If no numerical record is available within a visit window, the spleen volume will be considered as missing for the visit and imputation rules may be applied (see section 21.1).
2. If there is only one numerical record in a visit window, this will be used.
3. If more than 1 numerical record are available within the same visit window, the record closest to the Day 1 of the subsequent week will be used. For example, if there are multiple assessments for week 24, the one closest to Day 1 of week 25 will be used. If there are multiple records within the same distance from Day 1 of the subsequent week, the latest record will be used.

22.2 Study weeks for Total Symptom Score response (TSS)

Post-baseline TSS for a treatment week is calculated as the average of non-missing daily total symptom scores (using the MFSAF v4.0 or the MPN-SAF, depending on arm) over the week under scrutiny as depicted in Table 18 below. See section 22.3 for specifications to map the weekly averaged TSS data to an appropriate analysis visit window.

Table 18: Study week definition for total symptom score

Timepoint	TSS Assessment Day Relative to First Dose of CPI-610
Week -k (k=3, 4, 5, …)	Day (-k*7) to Day (-k*7+6)
Week -2	Day -14 to Day -8
Week -1 (Baseline)	Day -7 to Day -1
Week 1	Day 1 to Day 7
Week 2	Day 8 to Day 14
Week k (k=3, 4, 5, …, 23)	Day (k*7-6) to Day (k*7)
Week 24	Day 162 to Day 168
Week k (k=25, 26, 27, …)	Day (k*7-6) to Day (k*7)

Note: the study week for TSS as derived above is started from the date of first dose of study drug, independently of any other dates of subsequent doses of study drug.

22.3 Visit Windows for Total Symptom Score response (TSS) and Patient Global Impression of Change (PGIC)

Table 19 below illustrates the visit windows and the target study day for TSS data (as measured by the MF-SAF v4.0 or the MPN-SAF) and the PGIC data. The visit windows mapping also applies to end of treatment/end of study assessments.

Table 19: Analysis visit windows definition for total symptom score response (TSS) and the PGIC

Visit*	Target Study Day per Protocol	Analysis Visit Window (in days)	
		Lower Bound	Upper Bound
Week 12	Day 84	Day 43 (6*7+1)	Day 126 (18*7)
Week 24	Day 168	Day 127 (18*7+1)	Day 210 (30*7)
Week 12*k (k=3, 4, 5, …)	7*12*k	Day [(12*k-6)*7+1]	Day [(12*k+6)*7]

* Visit name for analysis purpose is used to report data in tables, figures and listings.

For TSS:

For TSS data that are summarized or analyzed by visit, the weekly averaged data (as calculated in section 22.2) is mapped to an appropriate analysis visit, using the following rules:

1. If no numerical record is available within a visit window, the TSS value will be considered as missing for the visit at stake.
2. If only one weekly average TSS value is available for a given visit window, this will be used.
3. If more than one weekly averaged TSS value is available within the same visit window, the weekly averaged TSS closest to Day 1 of the subsequent week will be used. For example, if there are multiple weekly averaged TSS values for week 24, the one closest to Day 1 of week 25 will be used. If there are multiple records within the same distance from Day 1 of the subsequent week, the latest record will be used.

For PGIC:

1. If no numerical record is available within a visit window, the PGIC value will be considered as missing for the visit at stake.
2. If more than one PGIC value is available within the same visit window, the PGIC closest to the week under scrutiny for the analysis (i.e., week 24 for PGIC at week 24; weeks 12, 36, 48 and 60 for the set of additional analyses on the PGIC) will be used; if there are multiple records within the same distance from the week under scrutiny, the latest record will be used.

See section 21.1 for imputation rules for TSS data and for PGIC data.

For the MFSAF TSS $_{28\ Days}$, the visit windows based on a 4-week approach and the target study day are illustrated below. The same rules as for TSS above apply for the mapping to an appropriate visit window.

Visit*	Target Study Day per Protocol	Analysis Visit Window (in days)	
		Lower Bound	Upper Bound
Week 4	Day 28	Day 15 (2*7+1)	Day 42 (6*7)
Week 8	Day 56	Day 43 (6*7+1)	Day 70 (10*7)
Week 4*k (k=3, 4, 5, …)	7*4*k	Day [(4*k-2)*7+1]	Day [(4*k+2)*7]

* Visit name for analysis purpose is used to report data in tables, figures and listings.

22.4 Visit Windows for Early Anemic Response rate and Anemic Response rate

No visits window will be applied due to the rolling period.

22.5 Visit Windows for Bone Marrow Fibrosis Grade

For local read data:

Table 20 below illustrates the visit windows and the target visit day for the analysis on bone marrow fibrosis grade data.

Table 20: Analysis visit window definition for Bone Marrow Fibrosis Local Read

Analysis Timepoint	Target Visit Day	Analysis Visit Window (in days)	
		Lower Bound	Upper Bound
Baseline	-1	NA	Day -1 (the day prior to Day 1)
Week 24	168	Day 85 (12*7+1)	Day 252 (36*7)
Week 48	336	Day 253 (36*7+1)	Day 420 (60*7)
Week 24*k (k=3, 4, 5…)	7*24*k	Day [(24*k-12)*7+1]	Day [(24*k+12)*7]

* Visit name for analysis purpose is used to report data in tables, figures and listings.

Data collected on all scheduled and unscheduled visits, including end of treatment/end of study assessments, will be mapped to an appropriate analysis visit window using the following rules:

1. If no numerical record is available within a visit window, the bone marrow fibrosis grade will be considered missing for the visit.
2. If there is only one numerical record in a visit window, this one will be used.
3. If more than 1 numerical record is available within the same visit window, the record closest to the target study day will be used; if multiple records within the same distance from the target study day are available, the latest record will be used.

For central read data:

Bone marrow fibrosis grade central read data will be summarized or analyzed by nominal visit, because the date of sample collection is not available from central read. See section 23 for the schedule of events.

Bone marrow fibrosis grade at week 24 from central read is defined as the last non-missing post-baseline result from central read on/prior to week 24 (i.e., Cycle 9, Day 1).

Bone marrow fibrosis grade central read and local read will be matched by the nominal visit name.

22.6 Unscheduled Visits

Unscheduled visits for splenic volume response data:

See section 22.1.

Unscheduled visits for early anemic response data and anemic response data:

See section 22.4.

Unscheduled visits for bone marrow fibrosis data:

See section 22.5

Unscheduled visits for IWG-MRT Response categoris data:

See section 22.7.

22.7 Visit Windows for IWG-MRT Response Categories

The table below illustrates the visit windows and the target study day for IWG-MRT response categories data.

Visit*	Target Study Day per Protocol	Analysis Visit Window (in days)	
		Lower Bound	Upper Bound
Week 24	Day 168	Day 85(12*7+1)	Day 252 (36*7)
Week 48	Day 336	Day 253 [(24*2-12)*7+1]	Day 420 [(24*2+12)*7]
Week 24*k (k=3, 4, 5, …)	7*24*k	Day [(24*k-12)*7+1]	Day [(24*k+12)*7]

* Visit name for analysis purpose is used to report data in tables, figures and listings.

IWG-MRT data collected on all scheduled or unscheduled visits, including end of treatment/end of study assessments, will be mapped to an appropriate analysis visit window using the following rules:

1. If no numerical record is available within a visit window, the IWG-MRT data will be considered as missing for the visit and imputation rules may be applied (see section 21.1).
2. If there is only one numerical record in a visit window, this will be used.
3. If more than 1 numerical record are available within the same visit window, the record closest to the target study day will be used. If there are multiple records within the same distance from the target study day, the latest record will be used.

23 Appendix: Schedule of Events

Table 21 below reports the schedule of events for the Phase 2 study - Arms 1, 2, and 3 (MF Expansion) and Arm 4 (ET Expansion). This is derived from section 6.2 of the study protocol - Tables 15, 16 and 17.

See section 6.1.4 for treatment cycle definition.

Table 21: Schedule of Events for Phase 2 - Arms 1, 2, and 3 (MF Expansion) and Arm 4 (ET Expansion)

	Screening	**Cycle 1**		**Cycle 2 & 3 and every odd numbered cycle** (i.e., 5, 7, 9, etc.)	**Cycle 4 and every even numbered cycle** (i.e., 6, 8, 10, etc.)	**EOT** (within 7 days of last dose of CPI-0610)	**Post-EOT 30-day safety follow-up**[a]	**LTFU** [a,b] Q12w ± 2 weeks	**EOS**[c]
Assessment (+/- days)	**Days** (-28 to	**Day 1**	**Day 14**	**Day 1** (+/- 3)	**Day 1** (+/- 3)				

	Prior to Dosing)								
Informed consent	X								
Inclusion/ exclusion criteria	X								
Demographics	X								
Medical history	X								
TB Testing (Arm 3 only)	X								
Physical examination	X[d, e]	X[d, e]		X[e]		X[e]			
MFSAF v4.0 (Arms 1, 2 and 3)	Completed every day for 7 days prior to Day 1 of each cycle[f]								
MPN-SAF (Arm 4 only)	X[f]	Completed on Days 15-21 of Cycles 1, 2, 4, 8, and every 4 cycles thereafter							
PGIC		X[g]		X[g]		X[g]			
ECOG performance status	X	X[h]		X[h]		X			
Vital signs	X	X[h, i]		X[h, i]		X[i]			
ECG (Arms 1, 2, and 3)	X	X[d]		X[d]		X			
ECG (Arm 4)	X	X[d]	X	X		X			
Transfusion documentation	X[j]	X[j]		X[j]	X[j]	X[j]		X[j]	X[j]
Coagulation	X[k]			X[h,k]		X[k]			
Hematology	X[d,k]	X[d, k]	X[k]	X[h, k]	X[h, k]	X[k]			
Clinical chemistry	X[d,k]	X[d,k]	X[k]	X[h,k]	X[h, k]	X[k]			
Serum Lipids	X[k]			See footnote k					
Pregnancy testing	X[k]	X[h,,k]		X[h,k]	X[h,k]	X[k]			
PK sampling		X[l]	X[l]	See footnote l					
Leukocyte gene expression (peripheral blood sample)		X[m]	X[m]	See footnote m					
Cytokine assessment (peripheral blood sample)		X[n]	X[n]	See footnote n		X[n]			
Viable cells (peripheral blood sample)		X[o]		See footnote o		X[o]			
Mutated allele burden (peripheral blood sample)		X[p]		See footnote p		X[p]			

Bone marrow biopsy	X[q]			See footnote r		X[s]			
MRI (or CT) scan (Arms 1, 2, and 3)	X[t]			See footnote t		X[s]		X	X
MRI (or CT) scan (Arm 4)	X[t]			See footnote t		X[t,s]			
CPI-0610 administration		Administered on Days 1-14 of each cycle							
Ruxolitinib administration (Arms 2 and 3 only)		Administered daily BID (see footnote u)							
Adverse events	X	Collected continuously while the patient is on study[v]					X[v]		
Concomitant medications	X	Collected continuously while the patient is on study[v]					X[v]		
AML (leukemic) Transformation		X[k, w]					X[a,w]	X[b,w]	X[w]
New anti-cancer therapy							X[x]	X[x]	X[x]
Survival Follow-up (Arm 3 only)							X	X	X

a. For Arms 1, 2 and 3: The "30-day safety follow-up visit" should occur 30 days (± 3 days) after the last dose of pelabresib or at the time of documented disease progression or, for patients initiating a new anticancer therapy, just prior to initiation of new therapy, whichever comes first. This visit may be conducted by telephone. Leukemic transformation and accelerated blast phase will be collected as AESI until 30-day safety follow-up or death, whichever comes first.

For Arm 4: The post-EOT 30-day safety follow-up visit should occur 30 days (± 3 days) after last study drug or at the time of documented disease progression or, for patients initiating a new anticancer therapy. Leukemic transformation and accelerated blast phase will be collected as AESI until 30-day safety follow-up or death, whichever comes first. The visit may occur by telephone.

b. For Arms 1, 2 and 3 only : Long-term follow-up (LTFU)

Splenic progression follow-up: Patients who discontinue treatment for reasons other than documented splenic progression or withdrawal from study should receive follow-up visits every 12 weeks (with a visit window of ± 2 weeks) starting from the EOT visit to document splenic progression by imaging every 12 weeks, until initiation of next anticancer therapy, progression, death or cutoff date, whichever comes first..

Transfusion requirements: Transfusions for the first 12 weeks starting from EOT will be collected. .For Arm 3: AML (leukemic) transformation follow-up: All patients will be followed up for AML (leukemic) transformation, records (by biopsy if applicable) will be collected every 12 weeks until documented AML transformation or the patients's death, whichever comes first. Follow up for AML transformation can be conducted by telephone if clinic visit is not planned.

c. For Arms 1, 2 and 3 only: if the subject is discontinued from LTFU, the reason of discontinuation should be recorded on EOS eCRF. An MRI (or CT) scan will be performed at the EOS visit only if splenic progression has not been previously documented or, in the absence of documented splenic progression, if imaging has not been performed within the previous 6 weeks. Transfusion requirement will be documented up to 12 weeks after last study drug..

d. The screening physical examination, ECG, hematology and clinical chemistry results do not need to be repeated on Cycle 1, Day 1 if they are conducted ≤ 72 hours before the first dose of CPI-0610.

e. Complete physical examination at screening, including height, weight, clinical signs and symptoms, and palpable spleen* length, measured with a ruler. *The edge of the spleen shall be determined by palpation, and measured in centimeters, using a soft ruler from the costal margin to the point of greatest splenic protrusion. The complete physical exam will include assessment of splenomegaly. Subsequent physical exams (within 72 hours prior to the start of Cycle 2, 3 and then every odd numbered cycle and at the EOT visit) may be targeted to areas of known disease and potential areas of MF/MPN involvement. Targeted physical examination must include weight and examination of the abdomen to assess the spleen length by palpation.

f. For Arms 1, 2 and 3: Symptom assessment via MFSAF v.4.0. During screening patients will complete the 24-hour symptom diary every day for 7 days prior to Cycle 1, Day 1 (preferred), or alternatively for any 7 consecutive days during the 28 days screening period. For each subsequent cycle, patients will complete the 24-hour symptom diary every day for 7 days prior to Day 1 of the cycle (i.e., Days 15-21 of the previous cycle). **NOTE:** patients who are on the ePRO devices will be prompted to fill out the MFSAF assessment daily. Sites will be notified and trained accordingly for implementation of the e-diary. For arm 4: Symptom Assessment via MPN-SAF. Patients will complete the assessment every day for the 7 days prior to Cycle 1 Day 1 (preferred), or alternatively for any 7 consecutive days during the 28 days screening period. In addition, patients will complete the assessment on Days 15 to 21 of Cycle 1, 2, 4, 8, and every 4 cycles thereafter.

g. The PGIC assessment should be completed prior to any other visit assessments on the visit day. The PGIC will be collected on Day 1 of Cycles 1, 2 and 3 and then every subsequent odd numbered cycle, and at the EOT visit. **NOTE** for arms 1, 2, and 3: patients may be requested to complete the symptom diary daily, if an electronic (e) system for symptom capture becomes available. Sites will be notified and trained accordingly for implementation of the e-diary.

h. Performed ≤ 72 hours before the start of the scheduled cycle, as indicated.

i. Vital signs must include: temperature, pulse, respiratory rate, and blood pressure.

j. All Arms: A complete transfusion history for the 12 weeks prior to enrolment will be taken during screening to include the date, type (e.g., whole blood, platelets, packed cells), number of units of the transfusions as well as the Hgb or platelet value at the time of the transfusion. Arms 1, 2, 3: Furthermore, transfusion history from medical records dating up to 1 year prior to study enrolment will be collected for patients enrolled in Arm 2A whenever available. An assessment of transfusion events will be collected on Day 1 of every cycle, at the EOT visit and at the first 12-week long-term follow-up visits for progression (for patients who discontinued for reasons other than disease progression). Arm 4: An assessment of transfusion events will be collected on Day 1 of every cycle, at the EOT visit

k. Coagulation parameters must include prothrombin time (PT), activated partial thromboplastin time (aPTT) and international normalized ratio (INR). PT, aPTT and INR will be determined during screening for all patients, ≤ 72 hours before the start of Cycle 2, 3 and then every odd numbered cycle of treatment as indicated, and at the EOT visit.

Hematology parameters must include a CBC with differential (i.e., RBC, Hgb, hematocrit, platelet count, total WBC count, neutrophils, eosinophils, basophils, lymphocytes, monocytes) and a peripheral blood smear (i.e., blast cells, nucleated erythrocytes, bands/stabs, myelocytes, metamyelocytes, and promyelocytes). Hematology will be obtained at screening, ≤ 72 hours before the start of each cycle of treatment, at Cycle 1 Day 14, and at the EOT visit. **NOTE:** Peripheral blood blasts need to be collected and assessed at every cycle.

Chemistry parameters must include sodium, potassium, total carbon dioxide, chloride, serum glucose, blood urea nitrogen (BUN), serum creatinine, total and direct bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), lactate dehydrogenase (LDH), uric acid, calcium, phosphorus, erythropoietin (EPO), C-Reactive Protein (CRP), iron*, iron binding capacity*, ferritin* and transferrin saturation*. The chemistry parameters will be obtained at screening, at Cycle 1 Day 14, ≤ 72 hours before the start

of Cycle 2, 3, and then every odd numbered cycle of treatment and at the EOT visit. **NOTE:** on Cycle 4 and every even numbered cycle thereafter, only liver function tests (LFTs) will be collected including total and direct bilirubin, AST and ALT. *Only required at screening, after 12 weeks of treatment (Cycle 5, Day 1), after 24 weeks of treatment (Cycle 9, Day 1), and then every 12 weeks (4 cycles) thereafter and at the EOT visit.

Serum lipids must include total cholesterol, cholesterol LDL, cholesterol high density lipoprotein (HDL) and triglycerides. Serum lipids will be obtained at screening, after 6 weeks of treatment (Cycle 3, Day 1), and then every 12 weeks (4 cycles) thereafter.

Pregnancy test is only required in women of child bearing potential. Should be performed at monthly intervals after EOT until 184 days after the last dose of study drug.

l. PK sampling follows the detailed tables outlined in Section 6.3.14.2 of the protocol. For Arms 1, 2 and 3: from Amendment 12 (v13) of protocol, PK sampling for the study has been completed.

m. A peripheral blood sample for leukocyte gene expression will be collected prior to dosing on Cycle 1, Day 1 and Day 14 and Cycle 3 Day 1 and at 4 hours after CPI-0610 dosing on Cycle 1, Day 1 and Day 14 and on Cycle 3 Day 1. In addition, samples will be collected on Day 1 of any cycle where the dose of CPI-0610 is changed (pre-dose and 4 hours after CPI-0610).

n. A peripheral blood sample for measurement of plasma cytokine concentrations and hepcidin will be collected prior to dosing on Cycle 1, Day 1, anytime on Cycle 1, Day 14, Day 1 Cycle 3, 5, 7 and 9 and at the EOT visit.

o. A peripheral blood sample (in 3 tubes) for collection of viable cells will be collected prior to dosing on Cycle 1, Day 1, and then anytime on Day 1 of Cycle 3, 5, 7 and 9 and at the EOT visit.

p. A peripheral blood sample for the assessment of mutated allele burden is collected prior to dosing on Cycle 1, Day 1, after 24 weeks of treatment (Cycle 9, Day 1) and then every 24 weeks (8 cycles) thereafter and at the EOT visit. From Amendment 12 (v13.0) of protocol, the collection of samples for allele burden assessment has been completed, except for the sample at EOT.

q. The bone marrow biopsy sample will be accepted as the screening sample if obtained within 3 months of Cycle 1, Day 1.

r. For arms 1, 2 and 3: bone marrow biopsy will be performed for fibrosis grading after 24 weeks of treatment (Cycle 9, Day 1) and then every 24 weeks (8 cycles) thereafter. **NOTE:** Following the bone marrow biopsy after 72 weeks (Cycle 25 Day 1), subsequent biopsies will be performed every 48 weeks (16 cycles). For arm 4: bone marrow biopsy will be performed after 48 weeks of treatment (Cycle 17, Day 1) and then yearly therafter for 3 years after the start of the study. For all arms: a window of ± weeks applies to these assessments.

s. The EOT bone marrow biopsy does not need to be collected if a biopsy has been performed within the previous 12 weeks. An MRI (or CT) scan will be performed at the EOT visit only if progressive disease (PD) has not been previously documented or, in the absence of documented PD, if imaging has not been performed within the previous 6 weeks for arms 1, 2, and 3, and within the previous 12 weeks for arm 4.

t. For arms 1, 2, and 3: An MRI (or CT) scan to measure spleen size will be performed during screening, after 12 weeks of treatment (Cycle 5, Day 1), after 24 weeks of treatment (Cycle 9, Day 1) and then every 12 weeks (4 cycles) thereafter. For arm 4: an MRI or CT scan will be performed at screening, after 24 weeks of treatment (Cycle 9, Day 1), after 48 weeks of treatment (Cycle 17, Day 1) and then yearly thereafter. For all arms: a window of ± 2 weeks applies to these assessments.

u. For Arm 3, the first ruxolitinib dose on Cycle 1 Day 1 should be administered after the 4th sample collection.

v. This information will be collected during clinic visits by study staff. Adverse events and concomitant medications should be collected for the first 30 days after the last dose of study treatment.

w. AML (leukemic) transformation can be assessed by either a bone marrow blast count of ≥ 20% or a peripheral blood blast content of ≥ 20% associated with an absolute blast count of ≥ 1 x 10^9 /L that persists for at least 2 weeks.

x. For Arms 1, 2 and 3 only.

24 Appendix: List of Standardized MedDRA Queries (SMQs) for COVID-19 related AEs

SMQs for identification of COVID-19 related AEs, with associated PTs, are provided in the following document:

- MANIFEST 1 List of SMQ_COVD-19.xlsx.

25 Appendix: Derivation Rules for Pharmacodynamic Data

IL-8 Gene Expression:

The derivation rules for the percent change in IL-8 gene expression analysis are detailed in the following document: MANIFEST-1 Pharmacodynamic Data Derivation Rules_v0.1.xlsx, sheet "IL8_Gene_Expression".

Blood Mutation Profiling:

The derivation rules for blood mutation profiling data are detailed in the following document: MANIFEST-1 Pharmacodynamic Data Derivation Rules_v0.1.xlsx, sheet "Blood_Mutation_Profiling".

26 Pre-specification of top-line results

In accordance with Constellation Pharmaceuticals data release process, top-line results are a set of approximately 15-to-25 Tables, Listings and Figures (TFLs) that fall within the top-line scope as detailed below. The set of top-line TFLs is required to be available based on the following timeline: within 5-to-10 business working days from Data Base-lock/Data extraction.

Top-line scope:

- Disposition and Analysis Sets;
- Baseline Characteristics and Demographics;
- Disease History;
- Treatment Exposure (Duration on treatment);
- PK/PD, depending on Study Objective;
- Primary and key-secondary Efficacy Endpoint(s);

- CTCAE Grade 3/4 TEAEs;
- TEAEs leading to discontinuation/Interruption/Dose change;
- SAEs;
- Deaths.

Based on what mentioned above, the table below pre-specifies the set of TFLs from the document" MANIFEST_1_List_of_TFLs_v5.0.xlsx" that are identified as top-line results for Study CPI 0610-02 (MANIFEST).

Table 22: Pre-specified TFLs for top-line results

TFLs number	Title	Analysis Population Set
14.1.1.2	Patient Disposition	Screened Patients
14.1.1.3	Patient Disposition	ITT
14.1.3.1	Summary of Demographic Characteristics	ITT
14.1.3.2	Summary of Baseline Disease Characteristics	ITT
14.1.8.1	Duration of Exposure to CPI-0610	SAF
14.1.8.3	Duration of Exposure to Ruxolitinib in Arm 2 and Arm 3	SAF
14.1.8.9	Duration of Exposure to Combined Treatment (CPI-0610 + Ruxolitininb) in Arm 2 and Arm 3	SAF
14.2.1.1	Summary of Rate of Conversion from Transfusion Dependence (TD) to Transfusion Independence in Cohort 1A, Cohort 2A and Arm 3	ITT
14.2.2.1	Time to Conversion from Transfusion Dependence (TD) to Transfusion Independence (TI) in Cohort 1A, Cohort 2A, and Arm 3	ITT
14.2.3.1	Duration of Red Blood Cell (RBC) Transfusion Independence (TI) in Cohort 1A, Cohort 2A, and Arm 3	ITT
14.2.7.1	Summary of Anemic Response Rate throughout the Study in Cohort 1B, Cohort 2B, and Arm 3	ITT
14.2.8.1	Duration of Anemic Response in Patients who are non-TD at enrolment in Cohort 1B, Cohort 2B and Arm 3	ITT
14.2.9.1	Time to Anemic Response in Patients who who are non-TD at enrolment in Cohort 1B, Cohort 2B and Arm 3	ITT
14.2.17.1	Summary of Splenic Response Rate (SVR35) at week 24 in Arm 1, Arm 2 and Arm 3	ITT
14.2.17.2	Summary of Percent Change in Spleen Volume from Baseline to Week 24 in Arm 1, Arm 2, and Arm 3	ITT
14.2.18.1	Summary of Splenic Response Rate (SVR35) at Week 12 in Arm 1, Arm 2, and Arm 3	ITT
14.2.18.2	Summary of Percent Change in Spleen Volume from Baseline to Week 12 in Arm 1, Arm 2, and Arm 3	ITT

14.2.19.1	Summary of Overall Splenic Response Rate (Overall SVR35) at Any Time in Arm 1, Arm 2, Arm 3	ITT
14.2.20.2	Duration of the Overall Splenic Response in Arm 1, Arm 2, and Arm 3	ITT
14.2.20.5	Reverse Kaplan-Meier Plot for Follow-up of Overall Splenic Response in Arm 1, Arm 2 and Arm 3	ITT
14.2.23.1	Summary of Percent Change in Total Symptom Score (TSS) from the MFSAF v4.0 from Baseline to Week 24 in Arm 1, Arm 2, and Arm 3	ITT
14.2.23.3	Summary of Total Symptom Score Response from the MFSAF v4.0 (MFSAF TSS50) at Week 24 in Arm 1, Arm 2 and Arm 3	ITT
14.2.34.6	Summary of the Distribution of Bone Marrow Fibrosis Change from Baseline to Week 24 by Local and Central Reads in Arm 1, Arm 2 and Arm 3	ITT
14.2.34.7	Summary of the Distribution of Bone Marrow Fibrosis Change from Baseline Over Time by Local and Central Reads in Arm 1, Arm 2 and Arm 3	ITT
14.2.34.8	Summary of the Distribution of Bone Marrow Fibrosis Change from Baseline to Week 48 from Local Reads in Arm 4	ITT
14.3.1.1	Summary of Treatment Emergent Adverse Events (TEAEs) by System Organ Class (SOC) and Preferred Term (PT)	SAF
14.3.1.5	Summary of NCI CTCAE Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) by System Organ Class (SOC) and Preferred Term (PT)	SAF
14.3.1.13	Summary of Serious Treatment Emergent Adverse Events (TEAEs) by System Organ Class (SOC) and Preferred Term (PT)	SAF
14.3.1.16	Summary of Most Frequent (at least 5 and 10% incidence) Treatment Emergent Adverse Events (TEAEs) by System Organ Class (SOC) and Preferred Term (PT)	SAF
14.3.1.57	Overall Summary of Adverse Events (AEs)	SAF
14.3.2.1	Summary of ALL Deaths, On-treatment Deaths and Post-treatment Deaths by Cause of Death	SAF

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STATISTICAL ANALYSIS PLAN- Phase 1

Study No.: 0610-02
Product Name: CPI-0610

A Phase 1/2 Study of CPI-0610, a Small Molecule Inhibitor of BET Proteins: Phase 1 (Dose Escalation of CPI-0610 in Patients with Hematological Malignancies) and Phase 2 (Dose Expansion of CPI-0610 with and without Ruxolitinib in Patients with Myelofibrosis)

Analysis plan for Phase 1: Dose Escalation of CPI-0610 in Patients with Hematological Malignancies

Version: Final 2.0

Date: 03 Aug 2021

Revision history

SAP Amendment 1: 10 Mar 2016 (INC Research)

SAP Draft 4.0: 27 Mar 2019 (Parexel)

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SAP Final 1.0: 20 Oct 2020 (Parexel)

SAP Final 2.0: 03 Aug 2021 (Parexel)

SIGNATURE PAGE – CONSTELLATION PHARMACEUTICALS

Declaration

The undersigned agree to the statistical analyses and procedures of this clinical study.

PPD

PPD **Date (DD Mmm YYYY)**

PPD **Biostatistics**

PPD

Date (DD Mmm YYYY)

PPD **Medical Director, Clinical Development**

SIGNATURE PAGE - PAREXEL

Declaration

The undersigned agree to the statistical analyses and procedures of this clinical study.

Prepared By:

PPD

Manager, Biostatistics

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ACTH	adrenocorticotropic hormone
AE	adverse event
ALL	acute lymphoblastic leukemia
ALT (SGOT)	alanine aminotransferase
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST (SGOT)	aspartate aminotransferase
AUC	area under the curve
AUL	acute undifferentiated leukemia
BET	bromodomain and extra-terminal
BID	twice daily
BUN	blood urea nitrogen
CBC	complete blood count
Cmax	maximum concentration
CML	chronic myeloid leukemia
CR	complete response/remission
CrCl	creatinine clearance
CRi	complete response/remission with blood count recovery
CRu	complete response, unconfirmed
CT	computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
cTn	cardiac troponin
DNA	deoxyribonucleic acid
EC50	50% effective concentration
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRCL	estimated creatinine clearance (by the Cockcroft-Gault formula)
eCRF	electronic case report form
EDC	electronic data capture
EOS	End of Study (visit)
EOT	End of Treatment (visit)
FAB	French-American-British
FDA	Food and Drug Administration
FISH	fluorescent *in situ* hybridization
GCP	Good Clinical Practice
GI	Gastrointestinal
GI50	concentration producing 50% inhibition of growth
GLP	Good Laboratory Practice
HCT	hematopoietic cell transplantation
HDPE	high density polyethylene
Hgb	Hemoglobin
HI	hematologic improvement
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
IC50	50% inhibitory concentration

ICH	International Conference on Harmonisation
IEC	independent ethics committee
IHC	Immunohistochemistry
IRB	institutional review board
IWG	International Working group
LDH	lactate dehydrogenase
LFTs	liver function tests
LPS	Lipopolysaccharide
LVEF	left ventricular ejection fraction
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis
MPN	myeloproliferative neoplasm
MRC	Medical Research Council
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NR	no response
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PK	Pharmacokinetics
PR	partial response/remission
PRBCs	packed red blood cells
PT	prothrombin time
QD	once daily
RBC	red blood cell
Rel	relapse
RNA	ribonucleic acid
SAEs	serious adverse events
SPD	sum of the product of the greatest perpendicular diameters
T1/2	elimination half-life
TLH	trilineage hematopoiesis
Tmax	time to maximum concentration
WHO	World Health Organization
β-hCG	beta-human chorionic gonadotropin

STATISTICAL ANALYSIS PLAN (SAP)

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data. It describes the main variables and populations, anticipated data transformation and manipulation methods. It also describes other details of the analyses not provided in the Clinical Study Protocol (CSP) of all data (source documents /electronic case report forms [eCRFs]) and captured electronically in DataLabs.

The analyses described are based on the final clinical study protocol for study number 0610-02 Amendment 7, Version 8.0, dated 07 September 2018. This Statistical Analysis Plan will include description of analyses for cohorts in **Phase 1**. Pharmacokinetic (PK) and pharmacodynamic (PD) analyses will be described in a separate SAP.

1 STUDY OBJECTIVES AND ENDPOINTS

1.1 Phase 1 Primary Objectives and Endpoints

Table 1.1 Phase 1 Study Primary Objectives and Endpoints

Objectives	Endpoints
To determine the maximum tolerated dose (MTD) of CPI-0610 and characterize its dose-limiting toxicities (DLTs) in patients with acute leukemia, myelodysplastic syndrome (MDS), or myelodysplastic/myeloproliferative neoplasms (MDS/MPN), and in patients with myelofibrosis (MF), when given once daily by cycle for 14 consecutive days and followed by a 7-day break.	The frequency of DLTs associated with CPI-0610 administration during the first cycle (first 21 days) of treatment

1.2 Phase 1 Secondary Objectives and Endpoints

Table 1.2 Phase 1 Study Secondary Objectives and Endpoints

Objectives	Endpoints
To characterize the safety and tolerability of CPI-0610	Adverse events and serious adverse events; changes in hematology and clinical chemistry values; changes in the physical examination, vital signs, electrocardiogram (ECG), echocardiogram (ECHO) and Eastern Cooperative Oncology Group (ECOG) performance status

To characterize the pharmacokinetics of CPI-0610 and profile its potential metabolites	$AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $AUC_{tau, ss}$, T_{max}, C_{max}, $T_{1/2}$, Vd/F, CL/F
To characterize the pharmacodynamic effects of CPI-0610 in peripheral blood leukocytes by assessing changes in the expression of genes sensitive to BET inhibition	Post-treatment changes from baseline in the expression of *MYC* and other sensitive genes in leukemic cells by qPCR or RNA Seq Post-treatment changes from baseline in the expression of *CCR2* and six additional genes in peripheral blood mononuclear cells (PBMCs) by qPCR
To characterize the pharmacodynamic effects of CPI-0610 in leukemic cells in the bone marrow	Post-treatment changes from baseline in expression of *MYC* and other genes that are sensitive to BET inhibition, assessed by measuring levels of their corresponding mRNA and/or protein Post-treatment changes from baseline in the expression of markers of cellular proliferation and apoptosis
To characterize any anti-leukemic, anti-MDS, anti-MDS/MPN or anti-MF activity associated with CPI-0610 treatment	Leukemia, MDS and MDS/MPN response as assessed by the investigator using the 2013 NCCN criteria for ALL, the 2003 Cheson criteria for AML, the 2006 modified International Working Group (IWG) criteria for MDS and MDS/MPN.

1.3 Phase 1 Exploratory Objectives and Endpoints

Table 1.3 Phase 1 Study Exploratory Objectives and Endpoints

CCI

2 STUDY DESIGN

2.1 Overall Study Design

This is a Phase 1/2, multi-center, open-label, dose escalation study (**Phase 1**) of CPI-0610 in patients with acute leukemia, MDS, MDS/MPN or MF and expansion study (**Phase 2**) of CPI-0610 as a single agent and in combination with ruxolitinib (a JAK inhibitor approved for the treatment of patients with MF) in patients with MF. The primary objective of **Phase 1** (dose escalation) is to determine the DLTs and MTD of CPI-0610 in patients with acute leukemia, MDS, MDS/MPN or MF.

In both phases of the study, CPI-0610 will be given once daily for 14 consecutive days followed by a 7-day break (1 cycle = 21 days), with 3-week cycles of treatment repeated as long as CPI-0610 is well tolerated and there is no evidence of disease progression.

During dose escalation, successive cohorts of 3-6 patients will be enrolled to increasing doses of CPI-0610. Following three initial dose doublings in patients with acute leukemia, MDS or MDS/MPN, the maximum increase in dose from one cohort of patients to the next will be guided by the modified Fibonacci series that automatically decreases the incremental increase in dose between cohorts, even in the absence of treatment-related toxicity. Dose escalation will continue until the MTD is estimated using a standard rule-based algorithm, commonly described as the "3+3 design". In this design the MTD is the highest dose that causes dose-limiting toxicity in less than 2 of 6 patients.

2.2 Schedule of Assessment

Study schedules, including all procedures to be performed during the study, are presented for the dosing regimen used during **Phase 1** (dose escalation) in Table 6-1 of the Protocol.

The screening period includes the 28 days before the first dose of CPI-0610.

In **Phase 1**, patients with acute leukemia, MDS, or MDS/MPN will have their disease assessed with peripheral blood counts and with bone marrow biopsy and aspiration at baseline, after the completion of every 2 cycles of treatment for the first 6 cycles, and thereafter following the completion of every 4 cycles of treatment.

Patients experiencing disease progression will have study treatment discontinued. In **Phase 1**, patients experiencing dose-limiting toxicity (DLT) will have therapy with CPI-0610 discontinued or, after recovery from the DLT, they may resume therapy at a lower dose of CPI-0610 if there is no evidence of disease progression.

Patients will be discontinued from the study if they withdraw consent, refuse treatment or request to stop treatment, fail to return for follow-up, begin an alternative medication, or if the investigator judges that further therapy with CPI-0610 is no longer in the patient's best interest for example, due to an adverse event, intercurrent illness, etc. Investigators also have the right to withdraw patients from the study for protocol violation or for administrative reasons.

3 STUDY POPULATION

Phase 1 (dose escalation) eligible patients must be adults (aged ≥ 18 years) who have one of the following hematologic malignancies: acute leukemia, including acute myelogenous leukemia (AML), acute lymphocytic leukemia (ALL), and acute undifferentiated or biphenotypic leukemia; chronic myelogenous leukemia (CML) in blast crisis; myelodysplastic syndrome (MDS); myelodysplastic/myeloproliferative neoplasms (MDS/MPN); or myelofibrosis (MF).

4 DETERMINATION OF SAMPLE SIZE

The number of patients enrolled in **Phase 1** of this study is driven by the dose escalation scheme and by the point(s) in the dose escalation scheme where DLT may occur. It is estimated that up to 44 patients with acute leukemia, MDS or MDS/MPN will be enrolled into to **Phase 1** (dose escalation).

5 RANDOMIZATION AND BLINDING

This is an open-label study. Randomization and treatment blinding are not applicable.

6 STUDY ASSESSMENT

6.1 Analysis Variables

6.1.1 Demographics and Baseline Characteristics

Patient demographics will be documented during screening and will include patient birth date, gender, ethnicity and race. The baseline characteristics will include height (cm) and weight (kg), and ECOG performance status.

6.1.2 Medical History

During the screening period the patient will have a complete medical history taken to include all medical conditions. The medical history will also include details on the cancer diagnosis with a description of all related prior therapies. Additionally, concomitant medications will be listed and will include all medications being taken at the time of screening.

6.1.3 Study Treatment

CPI-0610 will be administered by mouth once daily for 14 days followed by a 7-day break, with cycles of treatment repeated every 21 days. Cycles of treatment will be repeated as long as the patient's disease has not progressed or until precluded by toxicity.

6.1.4 Safety Variables

The following safety assessments will be performed:

- DLTs
- AEs and SAEs
- Laboratory assessments
- Electrocardiogram (ECG)
- Echocardiogram (ECHO)
- ECOG
- Physical examination
- Vital Signs
- Concomitant medications

6.1.4.1 DLTs

Dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed by the Investigator as unrelated to disease progression, intercurrent illness, or concomitant medications and that meets any of the criteria listed below in Table 2.

For the purpose of making dose-escalation decisions, all DLTs occurring during the first cycle of treatment with CPI-0610 must be included. DLTs occurring in subsequent cycles of treatment may also be considered when making decisions regarding dose escalation, particularly if they suggest that cumulative and/or late-occurring toxicity may limit dosing. Patients who discontinue from the study for reasons other than DLT (e.g., disease progression) before completing the treatment and evaluations needed to be evaluable for DLT will be replaced. Patients will be analyzed by the dose level to which they were originally assigned, including those who receive subsequent treatment at a lower or higher dose level.

Table 2 Definitions of Dose-limiting Toxicities

Toxicity	**Any of the following:**
Hematology: patients with acute leukemia, MDS, or MDS/MPN	The presence of CTCAE grade 4 neutropenia (ANC < 0.5 x 10^9/L) and/or grade 4 thrombocytopenia (<25 x 10^9/L) in the absence of any morphologic evidence of residual disease (acute leukemia, MDS or MDS/MPN), 21 or more days after suspending dosing with CPI-0610
Hematology: patients with MF	CTCAE grade 4 neutropenia (ANC < 0.5 x 10^9/L) occurring during CPI-0610 dosing and resulting in the omission of more than 1, 2 or 3 of the planned 7, 14 or 21 days of dosing CTCAE grade 4 neutropenia lasting for more than 7 days Platelets < 10 x 10^9/L of any duration ≥ CTCAE grade 3 thrombocytopenia (platelets < 50 x 10^9/L) with bleeding or any requirement for platelet transfusion
Renal	≥ CTCAE grade 3 serum creatinine (> 3.0 x baseline or > 3 x ULN)
Hepatic	≥ CTCAE grade 3 total bilirubin (> 3 x ULN)
	≥ CTCAE grade 3 ALT
Cardiac	≥ CTCAE grade 3
Other adverse events	≥ CTCAE grade 3 vomiting or CTCAE grade 3 nausea despite optimal anti-emetic therapy
	≥ CTCAE grade 3 diarrhea despite optimal anti-diarrhea treatment
	≥ CTCAE grade 3, except for the exclusions noted below[a]
	Other CPI-0610-related non-hematologic toxicities ≥ CTCAE grade 2 that, in the opinion of the investigator, require dose reduction or discontinuation of treatment with CPI-0610

Toxicity	**Any of the following:**
Treatment interruption	Treatment interruption caused by CPI-0610-related toxicity and resulting in the delivery of less than 6, 12 or 18 of the planned 7, 14 or 21 days of dosing in a cycle of treatment
Treatment delay	Treatment delay of more than 1 week (i.e., interval between the beginning of one CPI-0610 treatment cycle and the next by > 28 days for the 14 days on/7 days off schedule or the continuous daily dosing schedule; or by > 21 days for the 7 days on/7 days off schedule) because of inadequate recovery from the toxicity of the previous cycle of treatment (see Section 5.6 for retreatment criteria). In patients with acute leukemia, MDS or MDS/MPN treatment delays incurred because of hematologic toxicity are not dose-limiting unless there has been an absence of recovery of marrow function 21 or more days following the morphologic elimination of all disease from the bone marrow and peripheral blood.
Exceptions to DLT criteria[a]	CTCAE grade 3-4 elevations in alkaline phosphatase CTCAE grade 3-4 increases in serum uric acid without other associated physiologically significant effects
	CTCAE grade 3 increases in amylase and/or lipase in the absence of symptoms consistent with pancreatitis
	< 72 hours of CTCAE grade 3 fatigue

Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03 will be used for all toxicity grading.

Patients may receive supportive care (e.g., transfusion with packed red blood cells [PRBCs]0 and platelets) as per local institutional guidelines. The use of erythropoietin is permitted according to the American Society of Clinical Oncology (or other institutional) Guidelines.

Optimal therapy for nausea, vomiting and diarrhea will be based in institutional guidelines, with consideration of medications that are prohibited in this study.

When laboratory abnormalities form the basis for a DLT they should be confirmed by repeated testing with a new sample or assessment.

6.1.4.2 Adverse Events

AEs, TEAEs and SAEs:

Adverse events will be monitored throughout the study period beginning from the time of informed consent and for 30 days following the last dose of CPI-0610. All AEs and SAEs that occur during the reporting period will continue to be followed until the event resolves, the investigator assesses the event as stable, the event is determined to be irreversible, or the patient is lost to follow-up.

Treatment-emergent AEs are defined as any AEs that occurs after administration of the first dose of study treatment and through 30 days after the last dose of study medication, any event that is considered drug related regardless of the start date of the event, or any event that is

present at baseline but worsens in severity after baseline or is subsequently considered drug-related by the investigator.

An SAE is any AE occurring at any dose and regardless of causality that:

- Results in **death**.
- Is **life-threatening**. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form).
- Requires in patient **hospitalization or prolongation of existing hospitalization** (see clarification in paragraph below (Section 9.2) on planned hospitalizations).
- Results in **persistent or significant disability/incapacity**. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly/birth defect
- Is an **important medical event**. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in the definitions for SAEs.

AE Grade and Relationship

For both SAEs and non-serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration. Intensity of each AE, including any laboratory abnormality, will be determined by using the National Cancer Institute (NCI) CTCAE, Version 4.03. In those cases where the NCI CTCAE criteria do not apply, intensity should be defined according to the following criteria:

Table 3 Severity Assessment Terminology for Reporting Adverse Events (CTCAE v 4.03)

Event Intensity	Description	Grade
Mild	Awareness of sign or symptom but easily tolerated	1
Moderate	Discomfort enough to cause interference with normal daily activities	2
Severe	Inability to perform normal daily activities	3
Life-threatening or disabling*	Immediate risk of death from the reaction as it occurred	4

Death related to AE*		5

*must be reported as an SAE

Relationship of AEs to the investigational product (IP) will be assigned as follow: related (possibly, probably, or definite) or not-related (not-related or unlikely).

6.1.4.3 Clinical Laboratory Evaluations

Coagulation parameters

Prothrombin time (PT) (INR) and activated partial thromboplastin time (aPTT) will be determined during screening for all patients. Thereafter the PT (INR) and aPTT will be repeated only if clinically indicated. See Table 4 for INR CTCAE grade derivation.

Hematology

A CBC with differential white blood cell (WBC) count ("CBC with differential") will be obtained during screening, baseline, at least once weekly during each cycle of treatment with CPI-0610, and at the EOT and EOS visits.

The CBC with differential consists of the following: RBC, hemoglobin, hematocrit, reticulocyte count, platelet count, total WBC count, differential WBC count, neutrophils, Bands/stabs, eosinophils, basophils, lymphocytes, monocytes, and % blasts.

Peripheral blood smear consists of the following: total cell count, blast cells, nucleated erythrocytes, myelocytes, metamyelocytes, and promyelocytes.

Derivation of CTCAE grade for hematology tests are summarized in Table 4. If a test value in the normal range a grade of zero will be assigned.

Table 4 Derivation of CTCAE Grade – Hematological and Coagulation Tests

Tests	Direction	Grade 1	Grade 2	Grade 3	Grade 4
Coagulation Tests					
INR	↑	>1 - 1.5 x ULN; >1 - 1.5 times above baseline	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline	>2.5 x ULN; >2.5 times above baseline	
aPTT	↑	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN	
Hematological Tests					
Hemoglobin (g/dl, mmol/L or g/L)	↓	<LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN -100 g/L	<10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L;	Life-threatening consequences;
Platelet (/mm^3 or /L)	↓	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 -50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L
Neutrophils (/mm^3 or /L)	↓	<LLN - 1500/mm3; <LLN - 1.5 x10^9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x10e9 /L	<500/mm3; <0.5 x 10e9 /L

Tests	Direction	Grade			
		1	2	3	4
Lymphocyte (/mm^3 or /L)	↓	<LLN - 800/mm3; <LLN - 0.8 x10e9 /L	<800 - 500/mm3; <0.8 - 0.5 x10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x10e9 /L	<200/mm3; <0.2 x 10e9 /L

Note: 10e9 = 10^9; LLN = Lower Limit of Normal; ULN = Upper Limit of Normal

Clinical Chemistry

At **Phase 1**, A clinical chemistry panel will be obtained during screening, baseline, once weekly during each cycle of treatment with CPI-0610, and at the EOT and EOS visits.

The clinical chemistry panel consists of the following: sodium, potassium, carbon dioxide, chloride, serum glucose, blood urea nitrogen (BUN), serum creatinine, total and direct bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), lactate dehydrogenase (LDH), cardiac troponin (cTn), uric acid, calcium, phosphate, hepcidin, iron, iron binding capacity, ferritin and transferrin saturation.

Derivation of CTCAE grade for chemistry tests are summarized in the Table 5. If a test value in the normal range assign a grade of zero.

Table 5 Derivation of CTCAE Grade – Clinical Chemistry Tests

Tests	Direction	Grade			
		1	2	3	4
Sodium (mmol/L)	↓	< <LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L
Sodium (mmol/L)	↑	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Potassium (mmol/L)	↓	<LLN - 3.0 mmol/L	-	<3.0 - 2.5 mmol/L	<2.5 mmol/L
Potassium (mmol/L)	↑	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
Glucose	↓	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L
Glucose	↑	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8mmol/L	>500 mg/dL; >27.8 mmol/L
Creatinine	↑	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
Bilirubin	↑	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
Alkaline phosphatase (AKP)	↑	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
AST (SGOT)	↑	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALT (SGPT)	↑	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Uric Acid	↑	>ULN - 10 mg/dL (0.59 mmol/L)	-	-	>10 mg/dL; >0.59 mmol/L
Calcium	↑	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN- 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 -1.6 mmol/L;	Corrected serum calcium of >12.5 - 13.5mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L;	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L;

Tests	Direction	Grade			
		1	2	3	4
Calcium	↓	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 -0.9 mmol/L;	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L;	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L;
Phosphate	↓	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L

Note: 10e9 = 10^9; **LLN** = Lower Limit of Normal; **ULN** = Upper Limit of Normal

Pregnancy Testing

A serum beta-human chorionic gonadotropin (β-hCG) pregnancy test will be performed for women of childbearing potential during screening and at baseline. Both results must be negative before the first dose of CPI-0610 is given. In women of childbearing potential, the serum pregnancy test will be repeated ≤ 72 hours before the start of each new cycle of treatment. The pregnancy test will be repeated at the EOT visit.

ACTH Stimulation Testing

An adrenocorticotropic hormone (ACTH) stimulation test will be performed only in **Phase 1** before the patient receives his or her first dose of CPI-0610. In patients with acute leukemia, MDS or MDS/MPN, this test will then be repeated after the completion of every 2 cycles of treatment for the first 6 cycles, and thereafter following the completion of every 4 cycles of treatment.

The ACTH stimulation test consists of drawing blood for the measurement of serum cortisol concentrations before and then 30 and 60 minutes after the intravenous injection of 250 mcg of cosyntropin. The current criteria used to indicate normal adrenal function are a minimum serum cortisol concentration ≥18 to 20 mcg/dL (500 to 550 nmol/L) before or after ACTH injection.

6.1.4.4 Electrocardiogram (ECG)

A 12-lead ECG will be obtained as part of the screening evaluation.

On Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 1 Day 14 a 12-lead ECG will be performed prior to dosing with CPI-0610, and ECGs will be repeated at 1 hr (± 15 min), 2 hrs (± 30 min), 4 hrs (± 1 hr), and 6 hrs (± 2hrs) hours post-dosing.

An ECG will be performed ≤ 72 hours before the start of each new cycle of treatment.

6.1.4.5 Echocardiogram (ECHO)

ECHO will be obtained after every 2 cycles of treatment for the first 6 cycles, and thereafter following every 4 cycles of treatment.

An echocardiographic assessment of LVEF will be made during the screening evaluation. In patients with acute leukemia, MDS or MDS/MPN repeated echocardiographic assessment of LVEF will be made after the completion of every 2 cycles of therapy for the first 6 cycles, and thereafter following the completion of every 4 cycles of treatment.

6.1.4.6 ECOG Performance Status

ECOG performance status will be assessed during screening, ≤ 72 hours before the start of each new cycle of treatment, at the End of Treatment (EOT) visit and at the EOS visit (Phase 1 only).

6.1.4.7 Physical Examination

An assessment of signs and symptoms and a complete physical examination will be conducted during screening. The screening physical examination will record the patient's height and weight. The screening signs and symptoms assessment and physical examination may be used as the baseline assessments if they are conducted ≤ 72 hours before the first dose of CPI-0610.

An assessment of signs and symptoms and physical examination, including weight, will be conducted ≤ 72 hours before the beginning of each new cycle of treatment.

A signs and symptoms assessment and physical examination will be conducted at the EOT and EOS visits.

6.1.4.8 Vital Signs

Vital signs (blood pressure, heart rate, and oral temperature) will be taken during screening; prior to dosing and 1 hr (± 15 mins), 2 hrs (± 30 mins), 4 hrs (± 1 hr) and 6 hrs (± 2 hrs) after dosing on Cycle 1 Day 1; and ≤ 72 hours before the start of each new cycle of treatment.

6.1.4.9 Concomitant Medications and Supportive Therapies

All concomitant medications and supportive therapies will be recorded from screening through the end of the study.

6.1.5 Pharmacokinetic, Pharmacodynamic, and Biomarker Assessments

Pharmacokinetic (PK), pharmacodynamic (PD), and predictive biomarker analyses will be described in a separate document.

6.1.6 Efficacy Measurements

In **Phase 1** patients with acute leukemia, MDS or MDS/MPN disease response to treatment with CPI-0610 will be assessed through the evaluation of bone marrow aspirates and biopsies, along with CBCs and examination of peripheral blood films. In some cases, additional studies, e.g., examination of the CSF, may be needed to assess possible extramedullary disease. Response will be categorized by the investigator using the 2013 NCCN criteria for ALL, the 2003 Cheson criteria for AML, and the 2006 modified IWG criteria for MDS and MDS/MPN (please check the reference 44-46 in the CSP).

6.1.6.1 Acute lymphoblastic leukemia

National Comprehensive Cancer Network (NCCN) Guidelines, Version 1.2013, 03/25/2013:

Response Criteria for Blood and Bone Marrow:

- Complete remission (CR)
  - No circulating blasts or extramedullary disease
  - No lymphadenopathy, splenomegaly, skin/gum infiltration/testicular mass/CNS involvement
  - Trilineage hematopoiesis (TLH) and <5% blasts
  - Absolute neutrophil count (ANC) >1000/µL
  - Platelets >100,000/microL
  - No recurrence for 4 weeks

- CR with incomplete blood count recovery (CRi)
  - Recovery of platelets but <100,000 or ANC is <1000/µL

Overall response rate (ORR = CR + CRi)

- Refractory disease
  - Failure to achieve CR at the end of induction

- Progressive disease (PD)
  - Increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease

- Relapsed disease
  - Reappearance of blasts in the blood or bone marrow (>5%) or in any extramedullary site after a CR.

Response Criteria for CNS Disease:

- CNS remission: Achievement of CNS-1 status in a patient with CNS-2 or CNS-3 at diagnosis.

- CNS relapse: New development of CNS-3 status or clinical signs of CNS leukemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome.

➢ Classification of CNS status:

- CNS-1: No lymphoblasts in CSF, regardless of WBC count
- CNS-2: WBC <5/mcL in CSF with presence of lymphoblasts
- CNS-3: WBC ≥ 5/mcL in CSF with presence of lymphoblasts
- If the patient has leukemic cells in the peripheral blood and the LP is traumatic and WBC ≥5/mcL in CSF with blasts, then compare the CSF WBC/RBC ratio to the blood WBC/RBC ratio. If the CSF ratio is at least two-fold greater than the blood ratio, then the classification is CNS-3; if not, then it is CNS-2.

Response Criteria for Mediastinal Disease:

- CR: Complete resolution of mediastinal enlargement by computed tomography (CT).
- CR unconfirmed (CRu): Residual mediastinal enlargement that has regressed by 75% in the sum of the product of the greatest perpendicular diameters (SPD).
- PR: >50% decrease in the SPD of the mediastinal enlargement.
- PD: >25% increases in the SPD of the mediastinal enlargement.
- No response (NR): Failure to qualify for PR or PD.

Relapse: Recurrence of mediastinal enlargement after achieving CR or CRu.

6.1.6.2 Acute myelogenous leukemia

Cheson criteria, 2003:

➢ Complete Remission (CR)

The designation of CR requires that the patient achieve less than 5% blasts in a bone marrow aspirate sample that contains marrow spicules, with a count of at least 200 nucleated cells. There should be no blasts with Auer rods or persistence of extramedullary disease. A biopsy allows more bone marrow tissue to be examined and should be performed if spicules are absent from the aspirate sample. There is no requirement that the bone marrow achieve a certain degree of cellularity. A CR designation also requires that the patient have an ANC ≥ 1.0K/μL and a platelet count ≥ 100K/ μL. Neither the hemoglobin concentration nor the hematocrit has any bearing on remission status, although the patient must be independent of transfusions.

➢ Complete Remission with Incomplete Blood Count Recovery (CRi)

The designation of complete remission with incomplete blood count recovery (CRi) requires that all of the criteria for CR are met, but there is either residual thrombocytopenia (< 100K/ μL) or residual neutropenia (<1.0K/μL).

➢ Partial Remission (PR)

The designation of partial remission (PR) requires all of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts, to between 5% and 25% of the nucleated cells in the bone marrow. Therefore, if the pre-treatment bone marrow blast percentage was 50% to 100%, the percentage of blasts must decrease to a value between 5% and 25%. If the pre-treatment blast percentage was 20% to 49%, it must decrease by at least half to a value of more than 5%. A value of ≤ 5% blasts may also be considered a PR if Auer rods are present.

- Relapse (Rel)

Relapse after CR is defined as a reappearance of leukemic blasts in the peripheral blood or ≥ 5% blasts in the bone marrow not attributable to any other cause (e.g., bone marrow regeneration after therapy). The appearance of new dysplastic changes should also be considered relapse. In the setting of recent treatment, if there are no circulating blasts and the bone marrow contains 5% to 20% blasts, a repeat bone marrow performed at least 1 week later is necessary to distinguish relapse from bone marrow regeneration. In such instances the date of relapse is defined as the first date that more than 5% blasts were observed in the marrow. The reappearance or development of cytologically proven extramedullary disease also indicates relapse.

- Transformation to AML

Peripheral blood (percent of peripheral blood blasts) will also be used to monitor for conversion to AML throughout the study.

6.1.6.3 Myelodysplastic syndrome

Table 6.1**Error! Reference source not found.** and Table6.2**Error! Reference source not fo und.** describe the response criteria for altering the natural history of MDS and hematologic improvement, respectively.

Table 6.1 Proposed modified International Working Group response criteria for altering natural history of MDS

Category	Response criteria (responses must last at least 4 wks)
Complete remission	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines* Persistent dysplasia will be noted*† Peripheral blood‡ Hgb ≥ 11 g/dL Platelets ≥ 100 × 10^9/L Neutrophils ≥1.0 × 10^9/L† Blasts = 0%
Partial remission	All CR criteria if abnormal before treatment except: Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5% Cellularity and morphology not relevant
Marrow CR†	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment†

	Peripheral blood: if HI responses, they will be noted in addition to marrow CR†
Stable disease	Failure to achieve at least PR, but no evidence of progression for > 8 wks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following: Return to pretreatment bone marrow blast percentage Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence
Cytogenetic response	Complete Disappearance of the chromosomal abnormality without appearance of new ones Partial At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with: Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts 5%-10% blasts: ≥ 50% increase to > 10% blasts 10%-20% blasts: ≥ 50% increase to > 20% blasts 20%-30% blasts: ≥ 50% increase to > 30% blasts Any of the following: At least 50% decrement from maximum remission/response in granulocytes or platelets Reduction in Hgb by ≥ 2 g/dL Transfusion dependence
Survival	Endpoints: Overall: death from any cause Event free: failure or death from any cause PFS: disease progression or death from MDS DFS: time to relapse Cause-specific death: death related to MDS

Deletions to IWG response criteria are not shown.

To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

MDS indicates myelodysplastic syndromes; Hgb, hemoglobin; CR, complete remission; HI, hematologic improvement; PR, partial remission; FAB, French-American-British; AML, acute myeloid leukemia; PFS, progression-free survival; DFS, disease-free survival.

*Dysplastic changes should consider the normal range of dysplastic changes (modification).

†Modification to IWG response criteria.

‡In some circumstances, protocol therapy may require the initiation of further treatment (e.g., consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

Table 6.2 Proposed modified International Working Group response criteria for hematologic improvement

Hematologic improvement*	Response criteria (responses must last at least 8 wks)†
Erythroid response (pretreatment, < 11 g/dL)	Hgb increase by ≥ 1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wks compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation†
Platelet response (pretreatment, < 100×10^9/L)	Absolute increase of ≥ 30×10^9/L for patients starting with > 20×10^9/L platelets Increase from < 20 × 109/L to > 20×10^9/L and by at least 100%†
Neutrophil response (pretreatment, < 1.0×10^9/L)	At least 100% increase and an absolute increase > 0.5 × 109/L†
Progression or relapse after HI‡	At least 1 of the following: At least 50% decrement from maximum response levels in granulocytes or platelets Reduction in Hgb by > 1.5 g/dL Transfusion dependence

Deletions to the IWG response criteria are not shown.

To convert hemoglobin levels from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

Hgb indicates hemoglobin; RBC: red blood cell; HI: hematologic improvement.

*Pretreatment count averages of at least 2 measurements (not influenced by transfusions) ≥ 1 week apart (modification).

†Modification to IWG response criteria.

‡In the absence of another explanation, such as acute infection, repeated courses of chemotherapy (modification), gastrointestinal bleeding, hemolysis, and so forth. It is recommended that the 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

6.2 Analysis Populations

Safety analysis population is defined as all patients who receive any amount of study drug.

DLT population during **Phase 1** is defined as all patients who receive at least 85% of their planned dose of CPI-0610 in Cycle 1, unless interrupted by a DLT, and who have sufficient follow-up data to allow the investigators and sponsor to determine whether DLT occurred. Eighty-five percent of the planned dose is 12 of 14 doses with the 14 days on/7 days off schedule. Any patient who receives 1 to 11 doses of CPI-0610 in Cycle 1 and experiences a DLT in Cycle 1 will also be included in the DLT population.

Efficacy analysis population: Efficacy will be assessed in all patients in the Safety Analysis Population.

6.3 Statistical Analysis Methods

The statistical methods employed in this protocol will be primarily descriptive and graphical in nature. Continuous variables will be summarized using descriptive statistics [n, mean, standard deviation, median, minimum, and maximum]. Categorical variables will be

summarized showing the number and percentage (n, %) of patients within each classification. Safety and efficacy will be assessed in the appropriate treated populations. These data will be descriptively summarized by each dose level in Phase 1 and overall as appropriate.

6.3.1 Listings and Descriptive Statistics

Data for all enrolled patients who receive at least 1 dose of study drug will be presented in data listings. A patient who is enrolled but does not receive study drug will be included in those listings for which there is data but will be excluded from all data summaries. Data summaries will only include those patients that receive study drug.

Unless otherwise stated, the last non-missing observed measurement prior to the first dose of study drug(s) will be considered the baseline measurement.

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings:

- Present original observed values in listings. For any derived values from the observed values add one more decimal digit. For any sub-derived values (derived from derived values) add two more decimal digits.
- Estimates and confidence intervals will be presented to two decimal places.

6.3.2 Procedures for handling missing, unused, and spurious data

All available data will be included in data listings. Unless otherwise specified, no imputation of values for missing data will be performed. Percentages of patients with AEs or laboratory toxicities will be based on non-missing values.

Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures.

6.3.3 Statistical Significance Level

No formal statistical hypothesis is planned. Two-sided 95% confidence intervals will be used to describe the precision of the point estimates where appropriate.

6.3.4 Software

The tables and listings will be produced using SAS® Software (Version 9.2 or higher). The REPORT procedure (SAS PROC Report) will be used to produce all tables and listings.

All tables and listings will be produced to landscape orientation using Courier New 8pt font and will be incorporated into a MS Word document as a (RTF) rich text file (margins: top 1.5'', left, right, and bottom 1'').

6.3.5 Interim Analysis

No formal interim analysis is planned during Phase 1. Data will be evaluated on a continuous basis.

6.3.6 Patient Disposition, Eligibility, Protocol Deviation

Disposition of patients will be summarized for all enrolled subjects in **Phase 1**. The number and percentage of patients will be provided for those who are on treatment, those who discontinue treatment but are still in follow-up, and those who discontinue from the study. Further, patients who discontinue treatment and those who discontinue from the study will be summarized by the primary reason for discontinuation.

The date and time the informed consent was signed and patients with informed consent and re-consent data will be listed by dose group and patient. Patients who did not meet the eligibility criteria will be listed.

Deviations from the protocol will be assessed as 'minor' or 'major'. CSR reportable ("major") protocol deviations (PDs) are defined in accordance with ICH E3 as important PDs related to study inclusion or exclusion criteria, conduct of the trial, subject management or subject assessment resulting in the potential to jeopardize the safety or rights of the trial subjects or the scientific value of the trial.

All major PDs will be classified into the following categories, but not all deviations listed below will necessarily be declared a major PD:

- Adverse Event (AE)/ Serious Adverse Event (SAE)
- Disallowed Medications
- Inclusion/Exclusion criteria
- Informed Consent
- Investigational Product (IP) Admin/Study Treat
- Procedures/Tests
- Visit Schedule

Number and percentage of subjects with a major protocol deviation will be summarized by the category of deviation and dose group. The listing of protocol deviations by dose group and patient will be provided.

Major PDs may result in exclusions of subject from one or more analysis sets according to study specific PD codes specifications.

6.3.7 Demographic Data

Descriptive statistics and other baseline characteristics will be obtained in the safety analysis population for continuous variables including age, height, weight at baseline and BMI. The frequency and percentage of patients will be tabulated for categorical variables include age group (18-44 years, 45-64 years, ≥65 years), sex, race, ethnicity, and ECOG status. There are no treatment groups to be compared with respect to their baseline characteristics.

A by-patient listing of demographic information will also be provided by dose group and patient.

6.3.8 Cancer History and Previous Treatment

The frequency and percentage of disease diagnosis, history and status will be summarized by dose group and will be also listed by dose group and patient. Previous radiotherapy and systemic anti-cancer therapy will be listed.

6.3.9 Medical History

Medical history items will be coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 23.0 or higher version and summarized by system organ class (SOC) and preferred term (PT). Significant medical and surgical history data prior to dosing will be summarized by dose group and SOC/PT and will also be listed by dose group and patient.

6.3.10 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary drug (WHODD March 2021 or newer version) and will be summarized by dose group and Anatomical-Therapeutic-Chemical (ATC) therapeutic classification and preferred term (PT) and also be listed by dose group and patient. All prescription medications, over-the-counter medications, or alternative therapies taken within 28 days prior to the first dose of study drug through 30 days after the last dose of study drug will be recorded.

6.3.11 Dose Administration

Study dose administration will be presented by dose group. The number and percentage (n, %) of treatment cycles and number and percentage (n, %) of completed cycles patients received will be summarized. The descriptive statistics (n, mean, SD, median, min, and max) of treatment cycles and completed cycles patients will also be summarized.

The dose compliance will be summarized by cycle. The number and percent (n, %) of patients with 100%, ≥ 85%, ≥ 75% and <75% of dose compliance will be summarized. The descriptive statistics (n, mean, SD, median, min, and max) of dose compliance will also be summarized.

Treatment duration and dose intensity will be summarized using the descriptive statistics (n, mean, SD, median, min, and max).

Dose administration and exposure will include the following variables:

CPI-0610 dose compliance in a cycle = 100 * actual cumulative dose/planned total dose (daily dose * 14).

Overall CPI-0601 dose compliance = 100 * total cumulative dose/planned total dose (daily dose * 14 * number of the most recent cycle)

Treatment duration (in days) = last dose date - first dose date +1.

Total cumulative treatment duration (in days) = Sum of (max (14, (last dose date of cycle i – first dose date of cycle i + 1))), i=1 to the last cycle's number.

Actual dose intensity = cumulative actual dose (mg) / actual cumulative treatment duration (days).

Planned dose intensity = cumulative planned dose (mg) / planned cumulative treatment duration (days).
% Relative dose intensity = 100 × (actual dose intensity/planned dose intensity).

Cycle will be considered as completed if it lasted at least 14 days.

6.3.12 Efficacy Analysis

For **Phase 1**, analysis of efficacy measures will be descriptive.

A number of the variables described in Section 6.1.6 characterize the efficacy of CPI-0610 are primarily the disease response category based on the IWG MDS guidelines.

The number and percent (n, %) of disease response assessment will be summarized by following disease response category then by response criteria.

Disease response category includes:

- Acute Lymphoblastic Leukemia for blood and bone marrow
- Acute Lymphoblastic Leukemia for mediastinal disease
- AML or AUL
- MDS and MDS/MPN
- Hematologic Response

Response criteria includes:

- Complete Remission
- Complete Remission with Incomplete Blood Count Recovery
- Partial Remission
- Progressive Disease
- Relapse
- Stable Disease

The disease response assessment will also be listed by dose group, patient and visit.

The results of bone marrow aspirates and the results of bone marrow biopsies will be listed by dose group, patient, visit and category, separately.

6.3.13 Safety Analysis

6.3.13.1 DLTs

Summary of DLTs will be generated by SOC and PT for DLT population defined for **Phase 1.** DLTs for DLT population will also be listed by dose group, patient and SOC/PT.

Only DLTs in Cycle 1 will be included in the table summary.

6.3.13.2 AEs

The verbatim AE terms will be coded using the MedDRA, Version 23.0 or higher version and will be classified by SOC and PT.

Unless specified otherwise, summary counts of AEs will be the number of patients reporting adverse events and not the number of events reported. If the same AE (SOC or PT) is reported multiple times for the same patient, it will only appear once for that specified treatment and category in the summary tables.

For patients with multiple adverse events of the same preferred term and of different severities, the AE with the highest assessment of severity will be used in the summaries presented by severity.

For purposes of the summary tables, AEs will be classified as either being related to study drug or not related. For patients with multiple adverse events of the same preferred term and of different relationship, the AE with the strongest assessment of relationship will be used in the summaries presented by relationship.

The following AE Tables and Listings will be provided:

- TEAEs
- Drug-related TEAEs
- DLTs
- TEAEs $\geq$ 10% and $\geq$ 5%
- TEAEs of grade 3 or above
- Drug-related TEAEs of grade 3 or above
- Serious TEAEs
- Drug-related Serious TEAEs
- TEAEs Leading to Deaths
- TEAEs Leading to Study Drug Discontinuation
- Drug-related TEAEs Leading to Study Drug Discontinuation

In addition, Incidence of TEAEs and Serious TEAEs will be summarized by Custom MedDRA Queries (CMQ) and Preferred Term by treatment group (see Appendix).

6.3.13.3 Clinical Laboratory

Clinical lab values will be evaluated for each lab parameter by patient. Abnormal laboratory values will be graded by the CTCAE v 4.03 for gradable tests. Descriptive statistics (n, mean, standard deviation, median and range) of the parameters in hematology and chemistry and the changes from baseline will be presented by dose group. In the shift table based on being lower than a lower normal limit (worst low), a value above the upper normal limit will be considered as grade 0. The shift table for high worst is defined similar. Data from coagulation tests will be summarized and listed.

ACTH simulation result is defined as normal if minimum serum cortisol concentration >= 18 to 20 mcg/dL (500 to 550 nmol/L) at either of time points of Pre-ACTH injection, 30 Minutes Post-ACTH injection and 60 Minutes Post-ACTH injection. Otherwise, ACTH simulation result is defined as abnormal. The shift table of normal and abnormal ACTH simulation result from baseline will be summarized by dose group and visit. And ACTH simulation results will also be listed by dose group and patient.

Pregnancy results will be listed by dose group and patient.

6.3.13.4 12-Lead ECG

Baseline is defined as the mean of the last three non-missing triplicate assessments before dosing. The average value of multiple measurements at a visit will be used in the summary tables as well as in calculation of change from baseline.

Normal, abnormal non-clinically significant, or abnormal clinically significant ECGs will be summarized by dose group and visit.

Number and percentage of patients with maximum postdose QTcF values of <=450, >450 ms and <=480, >480 ms and <=500, and >500 ms, and maximal change from baseline values of <=30, >30 <=60ms, and >60 ms will be summarized by dose group and visit.

ECG results will also be listed by dose group, patient and visit.

6.3.13.5 Echocardiogram (ECHO)

Descriptive statistics for the actual values and the changes from baseline of echocardiogram over time will be tabulated by dose group and visit for measurements of Left Ventricular Ejection Fraction %, Left Ventricular Internal Diameter in Diastole (cm), Interventricular Septum Thickness in Diastole (cm) and Posterior Wall Thickness in Diastole (cm).

Normal, abnormal non-clinically significant, or abnormal clinically significant ECHO will be summarized by dose group and visit.

The data of echocardiogram will also be listed by dose group, patient and visit.

6.3.13.6 ECOG

ECOG performance will be summarized by dose group, visit and performance status. ECOG performance will be listed by dose group, patient and visit.

6.3.13.7 Physical Examination

Number and percentage of patients with abnormal results will be summarized by dose group, visit and body system. The data for physical examination will be listed by dose group, patient and visit.

6.3.13.8 Vital Signs

Descriptive statistics for the actual values and the changes from baseline of vital signs over time will be tabulated by dose group and visit. Vital signs will be listed by dose group, patient and visit.

7 REFERENCES

Protocol: A Phase 1/2 Study of CPI-0610, a Small Molecule Inhibitor of BET Proteins: Phase 1 (Dose Escalation of CPI-0610 in Patients with Hematological Malignancies) and Phase 2 (Dose Expansion of CPI-0610 with and without Ruxolitinib in Patients with Myelofibrosis). Version 8.5 dated 24 January 2019.

8 APPENDIX

CMQ	Preferred Terms
Abdominal pain	Abdominal pain, Abdominal pain Upper, Abdominal pain lower
Anemia	Anaemia, Haemoglobin decreased, Red blood cell count decreased
Asthenic conditions	Asthenia, Fatigue, Lethargy, Malaise
Bruising	Contusion, Ecchymosis, Hematoma, Increased tendency to bruise, Purpura, Vessel puncture site bruise
Dizziness	Dizziness, Vertigo, Balance disorder
Dyspepsia	Dyspepsia, Abdominal discomfort, Eructation, Epigastric discomfort
Leukopenia	Leukopenia, White blood cell count decreased, Neutropenia, Neutrophil count decreased, Febrile neutropenia, Lymphopenia, Lymphocyte count decreased, Monocyte count decreased
Lower respiratory tract infections	Lower respiratory tract infection, pneumonia, bronchitis, Lung abscess, Pulmonary sepsis, Tracheobronchitis, Pulmonary nocardiosis, Pulmonary tuberculosis, Lower respiratory infection bacterial, Lower respiratory infection fungal, COVID-19, COVID-19 pneumonia, Pneumonia influenzal, Suspected COVID-19
Musculoskeletal pain	Musculoskeletal pain, Myalgia, Arthralgia, Bone pain and Back pain
Neutropenia	Neutropenia, Neutrophil count decreased, Febrile neutropenia
Rashes	Rash, Rash erythematous, Rash macular, Rash maculo-papular, Rash popular, Rash pruritic, Rash vesicular, Viral rash, Nodular rash
Respiratory tract infections	Upper respiratory tract infection, Rhinitis, Sinusitis, Acute sinusitis, Chronic sinusitis, Tonsillitis, Tracheitis, Pharyngitis, Laryngitis, Nasopharyngitis, Nasal candidiasis, Oropharyngeal candidiasis, Upper respiratory tract infection bacterial, Upper respiratory fungal infection, Influenza, Viral upper respiratory

	tract infection, Lower respiratory tract infection, pneumonia, bronchitis, Lung abscess, Pulmonary sepsis, Tracheobronchitis, Pulmonary nocardiosis, Pulmonary tuberculosis, Lower respiratory infection bacterial, Lower respiratory infection fungal, COVID-19, COVID-19 pneumonia, Pneumonia influenzal, Suspected COVID-19
Stomatitis	Aphthous ulcer, Lip erosion, Lip ulceration, Mouth ulceration, Stomatitis
Thrombocytopenia	Thrombocytopenia, Platelet count decreased
Upper respiratory tract infections	Upper respiratory tract infection, Rhinitis, Sinusitis, Acute sinusitis, Chronic sinusitis, Tonsillitis, Tracheitis, Pharyngitis, Laryngitis, Nasopharyngitis, Nasal candidiasis, Oropharyngeal candidiasis, Upper respiratory tract infection bacterial, Upper respiratory fungal infection, Influenza, Viral upper respiratory tract infection
Urinary Tract Infections	Urinary tract infection, Pyelonephritis, Pyelonephritis acute