STATISTICAL ANALYSIS PLAN

STUDY N. : DSC/12/2357/45

A TWO-PART STUDY TO ASSESS THE SAFETY AND PRELIMINARY EFFICACY OF GIVINOSTAT IN PATIENTS WITH JAK2^{V617F} POSITIVE POLYCYTHEMIA VERA

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Statistical Analysis Plan Signature Page

Statistical Analysis Plan V2.2 (addendum) (Dated 21th March 2018) for a two-part study to assess the safety and preliminary efficacy of Givinostat in patients with JAK2^{V617F} positive Polycythemia Vera (Study N. DSC/12/2357/45; study protocol version 3.0, dated 29th July 2015).

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OUTPUT TEMPLATES SIGNATURE PAGE

Output Templates V2.2 (Addendum) (Dated 21th March 2018):

- **Part A:** Analyses to determine the Maximum Tolerated Dose (MTD);
- **Part B (I):** Stage I (Interim Analysis) of the Simon's 2-stage design (Primary evaluation of Response Rate)
- **Part B (II):** Stage 2 (Overall Analysis) of the Simon's 2-stage design (at the end of Part B).

For a two-part study to assess the safety and preliminary efficacy of Givinostat in patients with JAK2^{V617F} positive Polycythemia Vera (Study N.: DSC/12/2357/45; study protocol version 3.0, dated 29th July 2015).

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MODIFICATION HISTORY

Unique Identifier for this Version	Author	Significant Changes from Previous Authorized Version
V1	PPD	Not Applicable – First Version
V2	PPD	Added the text "In all cases, the medical judgment of the Investigator's is taken into account. In particular, if the Investigator's clinical response assessment – that takes into account the overall medical judgment of the specific patient's case - is not in agreement with the exact application of the clinico-haematological ELN or EUMNET response criteria , the Investigator's assessment will supersede the "mathematical" application of these criteria and used for analysis into study report." to the following sections: Section 16.3, Sections 17.2, 18.1 and 18.2. But section 16.11: sub section "EVALUATION OF PRELIMINARY EFFICACY ACCORDING TO THE REVISED ELN CRITERIA" and Section 19.1 the word updated from "clinico-haematological ELN or EUMNET response criteria " to "revised clinico-haematological ELN response criteria"
V2	PPD	Section 5.2: ITT population definition updated
V2	PPD	Section 15.1: Compliance derivation equation updated.
V2	PPD	Section 16.2. EFFICACY ASSESSMENT; the LOCF section removed because study is not using LOCF method to

		handle missing data.
V2	PPD	All Listing numbers changed from 16.1.x.x to 16.2.x.x to follow ICH E3 listing number guideline.
V2	PPD	The word of "exact method (as applicable)" added to the section 6.5
V2.1	PPD	The SAP section 10 updated to include following information in the table. Overall treatment group analysis for Part A tables and Figures, patients age group (< 60 years /≥60 years), Patients requiring phlebotomy, Patients with previous thrombosis history, patients with age ≥ 60 years and/or previous thrombosis history, Controlled hypertension (i.e. Normal ranges for systolic blood pressure: less than 120 mmHg, diastolic blood pressure: less than 80mmHg) and Number of patients with Pruritus, Headache, Microvascular Symptoms. Corresponding tables are updated for Part A and Part B II.
V2.1	PPD	SAP section 19.1: Additional analysis of patients without the symptom of headache, pruritus and microvascular symptoms (i.e MPN SAF Score =0) and number and percentage of patient with symptom score from 0 to 3, from 4 to 6 and more than 7 are added. Also patients rate with normalized WBCs (WBCs count ≤ 10 x 109/L), Patients rate with normalized platelets (platelets ≤ 400 x 109/L) and Patients rate with normalized haematocrit (haematocrit <45% without phlebotomy) are added. The following tables/figures are added.

		Tables 14.2.5.1, 14.2.5.2, 14.2.5.3, 14.2.5.4 and figures 14.2.1.18, 14.2.1.19, 14.2.1.20, 14.2.1.21, 14.2.1.22, 14.2.1.23, and 14.2.1.24 are added for Part A. Tables 14.2.6.3, 14.2.6.4, 14.2.6.5 14.2.6.6 and figures 14.2.1.19, 14.2.1.20, 14.2.1.21, 14.2.1.22, 14.2.1.23, 14.2.1.24 and 14.2.1.25 are added for Part BII.
V2.1	PPD	Section 20.4: Additional information of 'The number (n) and percentage (%) at baseline, Cycle 3 Day 28 and Cycle 6 Day 28 showed a Spleen Volume reduction ≥ 35%' is added. MedDRA dictionary (version 19.0) changed to MedDRA dictionary (version 20.1) and WHO-DRL Drug Dictionary (Version 01MAR2016) changed to WHO-DRL Drug Dictionary (Version 01SEP2017) Section 15.1: '+1' removed from the Per visit" Compliance calculation formula. Added the text 'Also for the last cycle compliance calculation this formula will be used as the last dose of study drug date considering from disposition page.'
V2.2 (Addendum)	PPD	1. Analysis performed for mathematical application of ELN response criteria (not agreed by the medical site team) and following tables are added. Part A: 14.2.1.1.1, 14.2.1.4.1, 14.2.1.7.1, 14.2.1.8.1, 14.2.1.9.1, 14.2.1.10.1 Part B: 14.2.1.1.1, 14.2.1.3.1, 14.2.2.1.1, 14.2.2.2.1, 14.2.2.3.1, 14.2.2.4.1, 14.2.9.1, 14.2.9.3, 14.2.2.7, 14.2.2.8. 2. The following tables/Figures are

		added:- Part A: T14.3.5.3, T14.3.5.4, T14.2.5.5, T14.2.5.6, F14.2.1.25, F14.2.1.26 and T14.1.21.2 modified. Part B: T14.3.5.3, T14.3.5.4, T14.2.6.7, 14.2.9.2, F14.2.1.26, F14.2.1.27 and T14.1.22.2 modified. 3. The following suffix number are added to TFLs outputs to differentiate the study parts in CSR: .a added for Part A, .bi added for Part B IA and .bii added for Part B II.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification
AUC	Area under concentration-time curve
$AUC_{(0-\tau)}$	Area under concentration-time curve over the dosing interval: from t=0 to t=12h
AUC_{last}	Area under concentration-time curve over the dosing interval: from t= 0 up to the last detectable concentration timepoint
b.i.d.	Bis In Die (twice daily)
BLQ	Below the lower limit of quantitation
BUN	Blood Urea Nitrogen
Ca	Calcium
CIs	Confidence Intervals
Cl	Chloride
Clast	Last detectable plasma concentration
Cmax	Maximal plasma concentration
cMPN	chronic Myelo-Proliferative Neoplasms
CMO	Contract Manufacturing Organization
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for AE
$C\tau$	trough concentration (Pre-dose levels on day 28 in the cycles of treatment)
CV	Coefficient of Variation
DLT	Dose Limiting Toxicity

ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELN	European LeukemiaNet
ET	Essential Thrombocythemia
EU	European Union
EUMNET	European Myelofibrosis Network
Hb	Haemoglobin
HBV	Hepatitis B Virus
HCT	Haematocrit
HCV	Hepatitis C Virus
HDACs	Histone deacetylases
HDACi	Histone deacetylases inhibitors
HDPE	High-density Polyethylene
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
ITT	Intent-to-treat
JAK2	Janus Kinase 2
$JAK2^{V617F}$	Janus Kinase 2 mutated at position 617
K	Potassium
LCM	Left Costal Margin
LDH	Lactate Dehydrogenase
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis
mg	Milligram
Mg	Magnesium
MPN-SAF	Myeloproliferative Neoplasm Symptom Assessment Form

MRI	Magnetic Resonance Imaging
msec	Millisecond
MTD	Maximum Tolerated Dose
Na	Sodium
NCI	National Cancer Institute
nM	Nanomolar
NR	No Response
NYHA	New York Heart Association
NQ	Not quantifiable
o.d.	Once Daily
PD	Pharmacodynamic
PLT	Platelets count
PMF	Primary Myelofibrosis
PP	Per-protocol
PR	Partial Response
PT	Preferred Term
PV	Polycythemia Vera
PK	Pharmacokinetics
QOL	Quality Of Life
qRT-PCR	Quantitative Real Time Polymerase Chain Reaction
QTc	QT interval corrected
RBC	Red Blood Cell count
RT-PCR	Real Time Polymerase Chain Reaction
RR	Response Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction

STAT5	Signal Transducers and Activators of Transcriptase 5
TdP	Torsades de Pointes
TEAE	Treatment-Emergent Adverse Event
t.i.d.	Ter In Die (three times daily)
T_{max}	Time of the maximal concentration in plasma
T_{last}	Time of the last detectable concentration in plasma
ULN	Upper Limit of Normal
WBC	White Blood Cell count
WHO	World Health Organization
WHO-DRL	World Health Organization-Drug Reference List

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1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis for the Study N.: DSC/12/2357/45 (hereinafter "Study").

It describes the data to be summarised and analyzed, including specifics of the statistical analyses to be performed. Deviations from methods described in the statistical analysis plan might appear. In case of such deviations the reason for the deviation will be stated in the final statistical report.

This Statistical Analysis Plan (SAP) is based on the Study protocol (version 1.0, dated 01st March 2013), Amended Protocol (version 3.0, dated 29 July 2015) and on two Amendments (Amendment 1, dated 23rd July 2013 and Amendment 2 dated 29th July 2015).

Notably, for the purpose of this document the name "Givinostat" is used to indicate the whole Study drug name "Givinostat hydrochloride monohydrate" (also known as ITF2357, i.e. its Sponsor's research code). Therefore, the dosages/concentrations of the Study drug are expressed as Givinostat hydrochloride monohydrate.

2. STUDY OBJECTIVES

In recent years several reports have documented that histone deacetylases inhibitors (HDACi) induce neoplastic cells to undergo growth arrest, differentiation and/or apoptotic cell death. Among these agents, Givinostat (Sponsor's research code: ITF2357) has most recently demonstrated effects on haematological parameters as well as constitutional parameters in patients with Polycythemia Vera (PV).

Preliminary signs of clinical activity in patients with JAK2 mutant cMPN, have been observed in two studies with Givinostat (Studies N.: DSC/07/2357/28 and DSC/08/2357/38). In these studies, the maximum administered dose of Givinostat was 150 mg per day which was generally well tolerated. Assuming a linear relationship between dose and efficacy, greater clinical efficacy could be expected with increased doses of Givinostat.

Since the Maximum Tolerated Dose (MTD) of Givinostat has not been defined previously, the first aim of the current Study (**Part A**, Phase Ib) is, therefore, to determine the MTD of Givinostat in patients with PV. This Study will investigate the safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) activity of Givinostat monotherapy. As such, the Study will characterize Dose Limiting Toxicities (DLTs) and MTD of Givinostat.

The second aim of the Study (**Part B**, Phase II) is to characterize the clinical efficacy of Givinostat at the MTD.

2.1. PRIMARY OBJECTIVE

This is a two-part, multicentre, open label, non-randomized, phase Ib/II study to assess the safety and tolerability, MTD and preliminary efficacy of Givinostat in patients with $JAK2^{V617F}$ positive PV.

Part A is the dose escalation portion of the Study; and, once the MTD is established, **Part B** is commenced where the preliminary efficacy of Givinostat in PV patients is to be established. Patients are enrolled either in **Part A** or **Part B** and transition from one part to the other is not allowed.

PART A

- To characterize the safety, tolerability and MTD of Givinostat in patients with PV.

PART B

- To evaluate the preliminary efficacy of Givinostat at the MTD after 3 cycles according to the clinico-haematological European LeukemiaNet (ELN) response criteria [1].
- To determine the safety and tolerability of Givinostat at the MTD after 3 cycles.

2.2. SECONDARY OBJECTIVES

PART A

- To evaluate the preliminary efficacy of Givinostat after 3 and 6 cycles of treatment according to the clinico-haematological ELN response criteria [1].
- To characterize PK.

PART B

- To evaluate the preliminary efficacy of Givinostat at the MTD after 6 cycles according to the clinico-haematological ELN response criteria [1].
- To determine the safety and tolerability of Givinostat at the MTD after 6 cycles.
- To characterize PK.

2.3. EXPLORATORY OBJECTIVES

PART A AND B

- To evaluate the effect of Givinostat on single parameters of the clinical-haematological ELN response criteria [1].
- To evaluate the effects of Givinostat on PD markers.
- To evaluate the effects of Givinostat on spleen size (by MRI or CT scan) in patients with confirmed splenomegaly at baseline.
- To evaluate the effects of Givinostat on disease-related quality of life.
- To evaluate the effect of Givinostat on $JAK2^{V617F}$ allele burden.
- To evaluate the reduction of the symptomatic treatment of pruritus.

PART B

- To evaluate the preliminary efficacy of Givinostat after 6 cycles of treatment according to the "**new**" ELN response criteria (i.e. the revised ELN response criteria).
- To evaluate the effect of Givinostat on single parameters of the "**new**" ELN response criteria (i.e. the ***revised*** ELN response criteria) [2].

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a two-part, multicentre, open label, non-randomized, phase Ib/II study to assess the safety and tolerability, MTD and preliminary efficacy of Givinostat in patients with $JAK2^{V617F}$ positive PV.

Part A is the dose escalation portion of the Study and, once the MTD has been established, Part B is commenced where the preliminary efficacy of Givinostat in PV patients will be established. Patients are enrolled either in **Part A** or **Part B** and transition from one part to the other is not allowed. Only PV patients from **Part A** assigned to the dose selected for **Part B** (MTD) can be counted towards the efficacy assessment in **Part B**.

Eligible patients for this Study have a confirmed diagnosis of PV according to the revised WHO criteria and the $JAK2^{V617F}$ positivity. Only if the enrolment in **Part A** is slow (i.e. < 5 patients enrolled in 3 months), eligibility for this part of the Study could be expanded to all patients with cMPN.

After providing informed written consent before undertaking any protocol-related procedure, a unique

patient identification code (i.e. patient screening ID which is a combination of his/her site ID, Study part ID and patient screening number, e.g. IT01-A01) is assigned to each patient which will identify the patient within his/her enrolment confirmation by Italfarmaco S.p.A. (Sponsor) or its designee (CRO) and can never be reused in case of screening failure. After the enrolment confirmation and the assignation of the dose level before the first drug intake, an unique patient identification code (i.e. patient ID which is a combination of patient screening number ID and dose level ID, e.g. IT01-A01-DL1) is assigned to each patient which willidentify the patient throughout his/her participation in the Study and can never be reused in case of premature drop-out.

Study therapy is administered in 28 day cycles. In fact, the "cycle" is defined as 4 weeks of treatment.

Disease response is evaluated according to the clinico-haematological ELN criteria [1] after 3 and 6 cycles (i.e. at weeks 12 and 24, respectively) of treatment with Givinostat for both parts of the Study. All phlebotomies performed in the first 3 weeks of treatment are not been counted to assess the clinico-haematological response.

The Study will last up to a maximum of 24 weeks of treatment. However, after completion of the trial, all patients achieving clinical benefit are allowed to continue treatment with Givinostat (at the same dose and schedule) in a long-term study (Study N.: DSC/11/2357/44), providing that the long-term study has already received all necessary approvals in that specific country and site, and the study has already been initiated in that particular site.

Safety is monitored at each visit throughout the entire duration of the Study. Treatment is administered on an outpatient basis and patients are followed regularly with physical and laboratory tests, as specified in the protocol (see Appendix A and paragraph 4.5.4 of the Study protocol version 3.0); in case of hospitalization, the treatment is continued or interrupted according to the Investigators' decision.

3.2. PART A

Part A is the dose escalation part of this Study, evaluating the safety, tolerability and MTD of Givinostat in patients with $JAK2^{V617F}$ positive PV.

In this part of the Study the first cycle of treatment is used to assess the safety and tolerability of Givinostat as well as PK/PD.

After the completion of the first cycle, the patients are treated for an additional 5 cycles.

Only PV patients from Part A assigned to the dose selected for Part B (MTD) can be counted towards the efficacy assessment in Part B.

The Dose Levels and the rules of escalation to the next dose are detailed in Sections 4.1.1.3 and 4.1.1.4

of the Study protocol version 3.0 (see pages 46 and 47).

3.2.1. DEFINITION OF DOSE LIMITING TOXICITY (DLT)

DLT is defined as the following drug-related toxicity:

- Grade 4 haematological toxicities, or
- Grade 3 febrile neutropenia, or
- Grade ≥ 3 non-haematological toxicities with exception of:
  a) Grade 3 diarrhoea without adequate supportive care lasting less than 3 days, and
  b) Grade 3 nausea or vomiting without adequate supportive care lasting less than 3 days, or
- Any drug-related SAE, or
- Any toxicity that is clearly not related to disease progression or intercurrent illness requiring interruption of dosing for more than 3 days during the first cycle.

The severity of the above mentioned events is graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE v. 4.03, 14th June 2010).

Only DLTs experienced during the first cycle of treatment are considered for dose escalation decisions. DLTs included all Adverse Events that are clearly not related to disease progression or intercurrent illnesses.

Patients who do not experience a DLT and miss more than 10% of the doses in Cycle 1 of Part A should be replaced (see paragraph 4.6.4 of the Study protocol version 3.0).

3.2.2. STUDY TEAM DEFINITION

The Study team included: selected Principal Investigator/s (i.e. Chairman and/or Principal Investigator/s who recruited the patients under discussion), the CRO's Medical Monitor, Sponsor's Medical Expert/s, Sponsor's Clinical Scientist and any other additional personnel, if necessary.

3.2.2.1. DOSE LEVELS (DLS) AND DOSE ESCALATION SCHEME

Dose escalation is conducted according to a standard 3+3 design, adopting a modified Fibonacci escalation schema [3, 4, 5]. Patients are enrolled in cohorts of 3 new patients (up to a maximum of 6) in rising dose levels (Table 1). Dose escalation to the next higher Dose Level (DL) can only occur after the third patient in the DL is followed for a minimum of 1 cycle after the first administration of study agent,

and the current dose is determined to have an acceptable safety profile according to the following rules summarised in Table 2.

Table 1 – Dose escalation scheme for Givinostat mono-therapy in *Part A*

Givinostat daily dose	Givinostat dose level (DL)	DL used primarily to assess
50 mg b.i.d.	DL0	Safety, PK, PD*
100 mg b.i.d.	DL1	MTD, PK, PD
150 mg b.i.d.	DL2	MTD, PK, PD
200 mg b.i.d.	DL3	MTD, PK, PD
150 mg t.i.d.	DL4	MTD, PK, PD
200 mg t.i.d.	DL5	MTD, PK, PD

** DL previously demonstrated as safe.*

The DL0 (i.e. 50 mg b.i.d.) was previously shown to be well tolerated in studies (see Section 6 "Effects in humans" of the Investigator Brochure Dossier related to ITF2357). Therefore, it is preferred to assign patients to the highest available dose level (i.e. DL1, DL2, DL3, DL4 and DL5) before assigning patients to DL0.

Intermediate Dose Levels (IDLs) and, consequently, additional DLs can be introduced to more accurately define the MTD.

Note that if a pregnancy occurs, the patient can be replaced and another patient in that DL should be recruited.

3.2.2.2. Dose Escalation Rules

In **Part A** each patient will receive Study drug at a specific DL. Once the first 3 patients of the first DL (i.e. DL1) are treated for 1 cycle, tolerability data are evaluated and a decision to escalate to the next dose is made.

Table 2 summarises the dose escalation rules for Givinostat in **Part A**.

Table 2 - Dose escalation rules for *Part A*

Number of patients with DLT at a given dose level	Action
0 out of 3	Enter 3 patients at the next DL.
1 out of 3	Enter at least 3 more patients at this DL and • *if 0 of these 3 new patients experiences DLT*, proceed to the next DL; • *if ≥ 1 of this group suffer DLT (for a total of ≥ 2/6 patients with a DLT)*, this DL exceeds the MTD and dose escalation is stopped. To further assess tolerability, 3 additional patients can be entered at the next lowest DL if only 3 patients were treated previously at that dose. Upon determination of the MTD, the Study should proceed directly to **Part B**.
≥ 2	Dose escalation should be stopped. This DL exceeded the MTD. To further assess tolerability, 3 additional patients can be entered at the next lowest DL if only 3 patients were treated previously at that DL and the Study should proceed directly to **Part B** of the Study.

At any time, if ≥ 2/3 or ≥ 2/6 patients at a given DL develop a DLT, it is acceptable to de-escalate to an intermediate, not previously studied dose (see **Table 1**), if evaluation of toxicity at such a dose is desired, in lieu of proceeding directly to **Part B** of the Study. If this approach is taken, 3 patients should be enrolled at the intermediate dose, and the aforementioned rules should be used to determine enrolment at this dose. If the decision is made to proceed directly to the efficacy portion of the Study (i.e. **Part B**), the efficacy part should be started at the next lower dose below where ≥ 2/3 or ≥ 2/6 DLTs are observed (i.e. the MTD dose level).

3.2.2.3. DEFINITION OF MTD

If 2 or more patients per DL experienced a DLT, dose escalation is terminated and the MTD is the next lower DL if no more than one out of 6 patients have a DLT at that level. Once all patients enrolled in **Part A** are treated for at least 1 cycle, the study team determine the MTD to be used in **Part B** based on the safety and tolerability profile of Givinostat observed as well as the PK and PD data, if applicable.

No intra-patient dose escalation is permitted prior to determining the MTD.

At that time, patients on treatment at lower DLs can be allowed to escalate their Givinostat dose up to the MTD for the remainder part of the study (**Part A**) at the discretion of the Investigator and, after the

Sponsor's written authorization. Of note, patients initially dosed at lower DLs that are allowed to escalate their Givinostat dose up to the MTD for the remainder part of the study (**Part A**), are to follow the dose modification rules of **Part B** (see paragraph 4.3.3.2 of the Study protocol version 3.0). Total daily dose can never exceed the MTD defined in **Part A** (i.e. 100 mg b.i.d.).

3.3. PART B

Part B is a multicentre, open label, non-randomized, phase II, cohort expansion Study to assess the preliminary clinical efficacy of Givinostat at the MTD in patients with $JAK2^{V617F}$ positive PV.

Patients enrolled in **Part B** started at the MTD defined in **Part A** (i.e. 100 mg b.i.d.), according to an optimized Simon's 2-stage design [6].

The dose of Givinostat is modified for Study protocol specified toxicities (see paragraph 4.3.3.2 of the Study protocol version 3.0).

3.4. TREATMENTS

3.4.1. TREATMENTS ADMINISTERED

Givinostat is supplied by the Sponsor or its designee as hard gelatine capsules for oral administration at the strength of 50 mg, and/or 75 mg, and/or 100 mg each.

Each capsule contains a granulate (obtained by wet granulation) composed of ITF2357, sodium starch glycolate, hydroxypropyl methyl cellulose (HPMC), sodium lauryl sulphate, lactose, magnesium stearate and colloidal silica.

The packaging consists of HDPE plastic bottles- closed with a PP screw cap, tamper evident - containing hard gelatine capsules of Givinostat. Each bottle contains:

- 30 capsules of 50 mg of Givinostat, or
- 30 capsules of 75 mg of Givinostat, or
- 15 capsules of 100 mg of Givinostat.

At each visit, patients receive a number of bottles sufficient to cover the period between two visits.

In ***Part A*** patients can be treated in DLs at the following starting daily doses of Givinostat:

- 50 mg b.i.d.;
- 100 mg b.i.d.;
- 150 mg b.i.d.;
- 200 mg b.i.d.;
- 150 mg t.i.d.;
- 200 mg t.i.d..

Intermediate Dose Levels (IDLs) and, consequently, additional DLs can be used to establish the MTD (for more details, see paragraph 4.1.1.3 of the Study protocol version 3.0).

Notably, the tested DLs to be considered for the MTD statistical analysis, are resumed in the **Table 1.1**.

Table 1.1 - Dose escalation of Givinostat performed in *Part A*

Givinostat daily dose	Givinostat dose level (DL)	DL used primarily to asses	Label for Tables, Listings and Figures (TLFs)
100 mg b.i.d.	DL1 (first three patients)	MTD, PK, PD	DL1
	DL1 (additional three patients)		DL1 expanded
2 capsules of 50 mg at the morning AND 1 capsule of 50 mg at the evening (i.e. 12 hours after)	DL6	MTD, PK, PD	DL6
50 mg b.i.d.	DL0	Safety, PK, PD*	DL0

** DL previously demonstrated as safe.*

No patient will be treated at the DL2, none at DL3, none at DL4, none at DL5 in **Part A**, as per dose escalation scheme describe in the Study protocol and also summarised in the section 3.2.2.1. of the present document.

In **Part B** patients are treated at the MTD of Givinostat established in Part A (i.e. 100 mg b.i.d., DL1).

Dose adjustments are permitted for patients who do not tolerate the protocol-specified dosing schedule, in order to allow these patients to continue the treatment with Givinostat (see paragraph 4.3.3.1 and paragraph 4.3.3.2 of the Study protocol version 3.0). The objective of the Givinostat dose adjustment rules described below is to optimize the response for each individual patient, avoiding specific drug-related toxicities.

Both in **Part A** and in **Part B**, patients self-administer daily Givinostat capsules at home as instructed by the Investigator (see paragraph 4.4.7.2 and paragraph 4.4.7.4 of the Study protocol version 3.0),

except for the first drug administration (i.e. Day 1 of the Cycle 1). Patients cannot take the morning dose of Givinostat on the day selected for their timed PK and PD assessments (see paragraph 4.5.3.2 and paragraph 4.5.3.3 of the Study protocol version 3.0). Study drug is administered in the clinic for these specific visits, in order to obtain pre- and/or post-dose plasma levels of Givinostat. On all the other days corresponding to study visits, patients should take the morning dose of Study drug prior to the visit.

In **Part A**, the lowest dosage of Givinostat that can be dispensed to the patients is 50 mg o.d.. In this case, the patient should take the Study drug each day in the morning with fluids and between meals (i.e. to take the study drug at least 2 two hours after the last meal, or no less than 1 hour before the meal). In all other possible dosages (i.e. 50 mg b.i.d, or 100 mg b.i.d., or 150 mg/die), patients should self-administer daily Givinostat capsules at home at morning and in the evening (i.e. after 12 hours) with fluids and between meals (i.e. to take the study drug at least 2 two hours after the last meal, or no less than 1 hour before the meal).

In **Part B**, the lowest dosage of Givinostat that can be dispensed to the patients is 50 mg b.i.d., while the highest dosage of Givinostat that could be dispensed to the patients is 100 mg b.i.d. In all the possible dosages (i.e. 50 mg b.i.d., 75 mg b.i.d., 100 mg b.i.d.), patients should self-administer daily Givinostat capsules at home at morning and in the evening (i.e. after 12 hours) with fluids and between meals (i.e. to take the study drug at least 2 two hours after the last meal, or no less than 1 hour before the meal).

Dose adjustments are permitted for patients who do not tolerate the Study protocol-specified dosing schedule, in order to allow to these patients to continue the treatment with Givinostat. The guidelines described in the Study protocol (see paragraph 4.3.3.2.1 and paragraph 4.3.3.2.2 of the Study protocol version 3.0) need to be followed. The objective of the Givinostat dose adjustment rules are to optimize the response for each individual patient, avoiding specific drug-related toxicities. Therefore, dose reductions or interruptions are mandated for specific toxicities and dose increases after an initial dose reduction are allowed in the case of inadequate efficacy at the reduced dosage.

Each dose modification is to be recorded on the Case Report Form (CRF).

3.4.2. METHOD OF ASSIGNING PATIENTS TO DOSE LEVEL

When a Study site has a patient ready to enroll, prior to dosing, the site have to compile a Request for Registration Form and send it to the Sponsor or CRO team, in order to obtain the patient ID.

This request is located in a specific section of the electronic CRF, which the site should complete only after having fully compiled all the previous screening sections, including medical history, patient's characteristics, a checklist related to the inclusion and exclusion criteria to verify the eligibility of the patient, etc.

The request for patient's registration contain the site ID (e.g. "IT01"), the Study part ID (i.e. "A" for **Part A** and "B" for **Part B**), the assigned patient screening number and the date of the request.

If the patient is eligible, the Sponsor or CRO confirm the enrolment of the patient assigning the related DL and the patient ID (i.e. the patient code after the enrolment confirmation) which is a combination of patient screening ID and dose level ID (e.g. "IT01-A01-DL1).

Once assigned, both the patient screening ID and the patient ID must not be reused for any other patient.

3.4.3. BLINDING

No blinding procedures are applicable as the Study is open label.

3.5. DETERMINATION OF SAMPLE SIZE

A standard 3+3 design adopting a modified Fibonacci escalation schema is used in **Part A** [3, 4, 5].

Sample size for **Part B** is discussed for the primary endpoint defined as the Overall Response Rate after 3 cycles. Simon's 2-stage design is employed in **Part B** [6] with the aim of testing the "null hypothesis" that RR ≤ 0.50 versus the "alternative" that RR ≥ 0.75. Response rate was assessed as defined in paragraph 6.2.5.2 of the Study protocol version 3.0. Overall, up to 28 patients are to be recruited, 12 patients being enrolled in Stage 1. PV patients enrolled at the MTD in **Part A** can be counted towards Stage 1.

Under the "null hypothesis" (if RR = 0.50), the expected total sample size is 18.2 patients, the probability of early termination at the end of Stage-1 is 0.613 and the probability of rejecting the "null hypothesis" is 0.081 (the target for the type-I error being 0.100).

Under the "alternative hypothesis" (if RR = 0.75), the probability of rejecting the "null hypothesis" in favor of the "alternative" is 0.902 (the type-II error being 0.098).

After testing the treatment on 12 patients in Stage 1, if 6 or fewer patients responded to the treatment, the trial should be terminated rejecting the "alternative" that RR ≥ 0.75. Otherwise, the trial should go on to Stage 2 enrolling a further 16 patients to a total of 28 patients.

If at the end of Stage-2, a total of 17 or fewer patients responded to the treatment, the "alternative hypothesis" that RR ≥ 0.75 should be rejected; alternatively, if 18 or more patients responded, the "null hypothesis" that RR ≤ 0.50 should be rejected.

Estimations were obtained from CRO proprietary software (based on SAS® 9.2) according to the

algorithm proposed by R. Simon [6].

3.6. SCHEDULE OF EVENTS

Schedule of events can be found in Section 4.5.4 of the Study protocol version 3.0.

Patient must be followed at the study centre according to the visit schedule and assessments outlined in the flow-charts presented in Appendix A of the Study protocol version 3.0.

3.7. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

CHANGES IN THE CONDUCT OF THE STUDY

Two amendments were implemented to the final protocol version 1.0, dated 01st March 2013.

The following changes were made in Amendment 1, dated 23rd July September 2013, with no impact on the planned statistical analysis, with the exception of the last point:

1. Clarification of the meaning of an "*effective* means of contraception for women of childbearing potential and men with partners of childbearing potential" (i.e. inclusion criterion n. 5) mentioning that the contraceptive methods will be used for up to 3 months after stopping the study treatment, as requested by the French Regulatory Authority.
2. Update of the patient numbering sections as per electronic CRF.
3. Correction of some typographic mistakes existing in the clinical Study protocol version 1.0 (dated 01st March 2013).
4. Addition of the exploratory endpoint of **Part B** the evaluation of the preliminary efficacy of Givinostat according to the "**new**" ELN response criteria (i.e. the **revised** ELN response criteria) [2].

The following changes were made in Amendment 2, dated 29th July 2015. Points 11 and 13-22 affect the planned statistical analyses:

1. Amendment of some wording in the *preclinical rationale* (paragraph 1.3 of the Study protocol) based on the most updated available information.
2. Update of the approved drugs for the treatment of PV and MF.
3. Addition of the neuromuscular disorders in the indications explored with Givinostat.

4. Clarification about the necessity to have received all necessary approvals in that specific country and site, performed the site initiation in that particular site, before starting the long-term study (Study N.: DSC/11/2357/44), that allows patients achieving clinical benefit in the Study to continue treatment with Givinostat (at the same dose and schedule) after completion of the Study.
5. Addition of the Contract Manufacturing Organization (CMO) as possible delegate for the management of the Study drug (e.g. secondary packaging, distribution to the sites).
6. Clarification of the meaning of "*any other investigational drug or device*" (i.e. exclusion criterion n. 19).
7. Specification of the instructions related to the Study drug administration and dispensing.
8. Clarification of the fact that no spleen evaluation should be performed in splenectomised patients, while the spleen evaluation was requested in all other patients in **Part B**, since the presence of splenomegaly was one of the parameters to evaluate as per primary objectives of **Part B** (i.e. according to the ELN response criteria [1]).
9. Explanation of the fact that, in case the patient completed the Study (i.e. performed all the evaluations requested to be done at Day 28 of Cycle 6), the evaluations performed at Cycle 6 Day 28 visit were also counted for the End of Study visit.
10. Specification of the fact that, in case the patient completed the Study (i.e. performs all the evaluations requested to be done at the Day 28 of Cycle 6) and she/he was eligible to continue the Study drug treatment in the long-term study (i.e. Study DSC/11/2357/44), the evaluation performed at the Day 28 of Cycle 6 visit of this Study could be also counted for the pre-treatment evaluations of the Study DSC/11/2357/44, provided that no difference in the evaluations was present between the two studies (e.g. haematological and biochemical evaluations).
11. Clarification that all efficacy analyses were conducted on this population and were based on the effective DL/daily doses of Givinostat at which each patient was treated.
12. Correction of typographic mistakes and better explanation of some sentences existing in the clinical study protocol version 2.0 (including Amendment 1, version 1.0, 23rd July 2013), in order to better detail the right procedures to be followed.
13. Update of the safety sections according to the more updated notification of Serious Adverse Event (SAE) Form (i.e.by electronic CRF), Adverse Events definition and the details of the Sponsor's Drug Safety Unit.
14. Update of the sections related to **Part B**, based on the definition of the MTD of Givinostat as chronic treatment in PV patients. Notably, in July 2015 the tolerability data related to the patients enrolled in **Part A** – i.e. the six patients treated at the Dose Level 1 (i.e. 100 mg b.i.d., DL1) and 3 patients treated at the Intermediate Dose Level (i.e. 150 mg/die, also defined

"DL6") - have been considered in order to define the MTD of Givinostat as chronic treatment in PV patients. Even if only one DLT was observed in the 6 patients treated at DL1 during the first cycle of treatment (i.e. a "*grade ≥ 3 non-haematological toxicity*" (dyspepsia), judged "*drug-related*" by the Investigator) and the escalation at higher DLs could be possible, the Study team agreed unanimously to consider the DL1 (i.e. 100 mg b.i.d.) as MTD of Givinostat to be used in **Part B** as chronic treatment in PV patients, considering the following points:

- Givinostat was a chronic treatment for PV patients in the current schedule;
- The observed PLT decrease;
- The knowledge of the safety profile of HDACi and, in particular, of Givinostat (i.e. thrombocytopenia was a side-effect);
- It could be preferable/ethical to avoid exposing 3 patients to the higher dosage (i.e. 150 mg b.i.d., DL2) that, as above reported, will be reasonably untollerated by the patients.

Therefore, the dosage to use in **Part B** as established in **Part A** by the Study team, i.e. 100 mg b.i.d., was defined as the MTD of Givinostat taking into account the chronic schedule of the study drug as prescribed in this current study.

15. Update of the dose modification rules to be applied in **Part B** and in **Part A** for patients who may be allowed to escalate their Givinostat dose up to the MTD for the remainder of the Study (**Part A**) at the discretion of the Investigator and Sponsor.
    The dose modifications rules to be applied in **Part B** have been updated based on the data related to the patients enrolled in **Part A** of this Study and to the results obtained in previous studies with Givinostat on cMPN. The objective of the updated Givinostat dose adjustments rules are to optimize the response for each individual patient, avoiding specific drug-related toxicities. Therefore, dose reductions or interruptions are mandated for specific toxicities and dose increases after an initial dose reduction are allowed in case of inadequate efficacy at the reduced dosage in absence of specific toxicities.
    Notably, the same dose modification criteria could be followed by patients initially dosed at lower dose levels in **Part A** that, after the definition of MTD, could be allowed to escalate their Givinostat dose at MTD for the remainder part of the study (**Part A**) at the discretion of the Investigator and Sponsor.
16. Addition of the strength of 75 mg.
17. Addition of PD evaluations, performed using an aliquot of the PK samples.
18. Clarification of the calculation of eGFR (i.e. a derived biochemical parameter) in accordance with the Mayo Clinic Quadratic Equation, as agreed with the German Regulatory Authority.
19. To allow the evaluation of Urea (in spite of BUN) in accordance with the site-specific clinical practice.

20. Addition of the recommendation to perform two additional ECG evaluations over a brief period (i.e. 5 minutes between each recording), if the first ECG evaluation demonstrates a prolonged QTc interval (i.e. a QTc interval ≥ 450 msec).
21. Clarification of the fact that in **Part B** it is recommended that patients should be told to arrive after an overnight fast of at least 8 hours at all Study visits that requested a blood test.
22. Addition of the collection of a blood sample for the quantitative RT-PCR evaluation of $JAK2^{V617F}$ mutational status on peripheral blood granulocyte at the following Study visits of **Part B**: Day 28 of Cycles 1, 2, 4 and 5.

CHANGES IN THE PLANNED ANALYSIS

No changes to analysis from the Final version of the Protocol (version 3.0, dated 29 July 2015) are planned with the exception of the use of the SAS software, version 9.2 or higher, (instead of the StatXact-4 software) to compute Exact/Nonparametric 95% CIs.

4. PLANNED ANALYSES

The following analyses are planned:

A. Part A: Analyses to determine the Maximum Tolerated Dose (MTD);

B. Part B (I): Stage I (Interim Analysis) of the Simon's 2-stage design (Primary evaluation of Response Rate)

Interim analysis will be performed on the 12 patients of the first stage of part B. If seven or more responses will be observed in the first stage of part B, further 16 patients will be enrolled in the second stage of part B. If six or fewer responses will be observed during the first stage then the study will be stopped. Futility will be assessed in 12 patients after 3 cycles.

The Interim analysis will evaluate preliminary efficacy and safety and tolerability of Givinostat at the MTD after 3 cycles in 12 patients. Exploratory endpoints analysis will also be included with available data after 3 cycles.

C. Part B (II): Stage 2 (Overall Analysis) of the Simon's 2-stage design (at the end of Part B).

Final analysis will be performed in all 28 patients enrolled in two stages of part B after 6 cycles.

No formal DB lock is planned neither for the 1st Cycle of Part A not for Stage 1 (Simon's 2-Stage design) of Part B of the study.

Three different Output Templates will be presented for the 3 sets of analyses.

5. ANALYSIS SETS

Agreement and authorization of patients included/excluded from each analysis set will be conducted prior to the database lock of the study during the Data Review Meeting.

The analysis sets are defined distinctly for each of the 3 planned analyses.

The number and percentage of the patients included in the analysis populations will be reported in a table showing the reason of exclusion for all patients enrolled into study. A listing of reasons of exclusion from analysis population will be provided.

Patients who sign an informed consent form but who do not start Study treatment for any reason, will be considered as "Screening Failures". For these patients, a separate Table will be produced including the primary reason for screen failure and patient's demographic information as per electronic CRF.

5.1. SAFETY ANALYSIS SET (SAF)

The Safety analysis set will include all enrolled patients who receive at least one dose of study medication. All safety analyses will be conducted on this population.

5.2. INTENT-TO-TREAT ANALYSIS SET (ITT)

The Intent-to-treat analysis set will include all recruited patients who receive at least one dose of study medication and from whom at least one post-baseline efficacy measurement is obtained.

Of note, patients who dropped the study due to drug-related TEAE(s) before that the post-baseline efficacy measurement is obtained (i.e. at C3D28 and/or at C6D28), will be considered in the ITT analysis set; in these cases, the post-baseline efficacy measurements (i.e. at C3D28 and/or at C6D28) will be considered as "No Response", even if these assessments were not performed.

In addition, patients who have performed the visit when the post-baseline efficacy measurements (i.e. at C3D28 and/or at C6D28) had to be performed, but for which the following conditions will happen, will be excluded from the ITT analysis set:

- HCT > 45% or HCT ≤ 45% with phlebotomy(ies), AND
- at least 2 out of 4 assessments of the following will be not performed:

  a) WBC count;

b) PLT count;

c) Spleen evaluation by CT scan or MRI;

d) Disease-related assessment by MPN-SAF.

This is due to the fact that is not possible to define a clinico-haematological response as per ELN response criteria in these cases.

All efficacy analyses will be conducted on this population and will be based on the *effective/actual* DL/daily doses of Givinostat at which each patient has been treated.

5.3. PER PROTOCOL ANALYSIS SET (PP)

In order to assess the robustness of the efficacy analysis, the analysis of the efficacy end-point will be repeated on the Per Protocol (PP) analysis set. The Per-protocol analysis set will include all ITT patients who receive at least 14 daily doses without interruptions, and without any major deviation from the protocol procedures.

5.3.1. PROTOCOL DEVIATIONS

Protocol deviations to be reviewed will include, but will not be limited to, patients who:

- Did not meet inclusion/exclusion criteria or eligibility not adequately verified.
- Received disallowed concomitant medications pre- and/or post-treatment.
- Developed withdrawal criteria but were not withdrawn.

According to Quintiles SOPs the PDs are classified as Minor, Major and Critical. Starting from 1st March 2016, the categorization changed into Minor, Important (for Major) and Priority (for Critical).

In order to comply with the Protocol requirements, the categorization of 'Critical', 'Important' and 'Priority' will fall into the 'Major' one.

A. **<u>Major protocol deviations</u>** to be reviewed will include, but will not be limited to, the following groups:

1. Entry criteria:

- Any "no" response to inclusion criteria and/or any "yes" response to exclusion criteria and patient was subsequently enrolled.

NOTE: only in case of previous written Sponsor authorization this type of deviation can be considered

as 'Minor'.

2. Investigational Medicinal Product:
    - Investigational Product dosing error: in case the patient takes a dose of IP that is different from the assigned dose (example: dose level, DL0, DL1, DL6 or MTD as defined at the end of study Part A).
    - Enrolled out of DL - NOTE: only in the case of previous written Sponsor authorization to have the patient enrolled on cohort DL0 this is not considered as a protocol deviation.
    - Part A (between C2D1 and C6D28) and Part B: Non-compliant with IMP usage (under 80%). According to the protocol "A patient will be considered sufficiently compliant with Givinostat treatment if he/she has taken at least 80% of the prescribed dose over the total duration of study drug dosing".
    - The site dispensed the used IMP stored out of the following storage conditions described in the IMP handling manual, to the patient without the Sponsor's written authorization: (i) IMP storage temperature ≥ 30°C and ≤ 40°C for ≥ 30 days, or (ii) IMP storage temperature > 40°C
    - Incorrect IMP dispensation to a patient: (i) in case the site incorrectly assign a dosage different from the one approved by the Sponsor at the time of enrollment (example: dose level, DL0, DL1, DL6 or MTD as defined at the end of study Part A), or (ii) in case the site performed a dose escalation not predicted by the study protocol.

3. Informed Consent:
    - Patient did not sign Main ICF.
    - ICF is signed after study procedure was done, except for invasive procedures performed before the ICF signature as clinical practice AND, anyway, only after the Sponsor's written authorization to be obtained before the first drug intake.

4. Concomitant Medications:
    - Patient used prohibited medication(s) during the study course.

5. Study Procedures:
    - SAEs not reported in according to the correct timelines.

B. **<u>Minor protocol deviations</u>** to be reviewed will include, but will not be limited to, the following groups:

1. Entry criteria:
   - Patient enrolled without all data and results available to evaluate the inclusion and exclusion criteria, or not following the correct enrollment protocol procedures.
   - Enrollment of the patient with the local laboratory report for confirming the $JAK2^{V617F}$ positivity before receiving the confirmation from the central laboratory and without the Sponsor's written authorization.

2. Investigational Medicinal Product:
   - The patient has assumed the IMP out of the procedures described in the IMP Handling manual.
   - IMP accountability not done or not fully completed by the site.
   - Missed IMP dose that does not affect the 80% of IMP compliance.

3. Visit Schedule:
   - Screening visit performed outside approved protocol window (28 days +/- 7 days). In fact, patient must be medically stable on the basis of physical examination, medical history, and vital signs performed at screening [within 28 days before randomization to Day 1]. If there are abnormalities, they must be consistent with the underlying illness in the study population.
   - End of Study Visit (EOS) not performed or performed more than 7 days after last drug intake, except for completers patients.
   - Patient visits performed outside approved window, except in case of the Sponsor's written authorization (for example, the patient is in vacation and the study visit should be performed 2 days before his/her coming back).
   - Patient visits not fully performed as per study protocol.
   - Patient(s) miss an entire visit.

4. Informed Consent:
   - Incorrect version of ICFs signed.
   - In case of pregnancy, the patient – if female – or the patient partner – if the patient is a male - has not signed the Pregnancy ICF and the pregnancy data have been collected.
   - Missing date of ICFs.
   - Site personnel who signed ICFs is not on Site Personnel Signature Delegation Log and/or not authorized by PI to sign ICFs.
   - Bone Marrow (BM) consent not provided, but BM histological evaluation done.
   - Pregnant Partner ICF obtained although the partner of the patient IS not pregnant.
   - Latest version of non-substantial ICFs not signed by the patient at the first study visit

once the ICFs is available at site.
- IEC/IRB contact details or site's contact details not included on ICFs.
- Patient did not directly add his/her name on the ICFs space near to the signature.

5. Study Procedures:
   - Lack of adherence to delegation requirements.
   - Bone Marrow consent provided, but sample not collected by the site.
   - SAEs not appropriately reported Systemic lack of Principle Investigator oversight of safety data.
   - Not collecting samples related to primary efficacy variables: haematology samples not collected at cycle 3.
   - Study procedures needed for the primary objectives and primary endpoints not done: haematology samples not collected, spleen evaluation not done, MPN-SAF QOL and Questionnaire not completed at all at cycle 3, ECG including QTc determination not completed at cycle 3. Study procedures needed for the secondary objectives and secondary endpoints not done: haematology samples not collected, spleen evaluation not done, MPN-SAF QOL Questionnaire not completed at all, PK sample not collected at cycles 3 and 6 and Bone Marrow histological evaluation not done at cycle 6.
   - Study procedures needed for the exploratory objectives and endpoints not done: haematology samples not collected, PD samples not collected, spleen evaluation not done, MPN-SAF QOL Questionnaire not completed at all, $JAK2^{V617F}$ not collected according to the protocol and Bone Marrow histological evaluation not done.
   - A negative urine B-human chorionic gonadotropin (B-hCG) pregnancy test not collected at screening visit for patient, if women of childbearing potential.
   - Delegation log not up to date prior to study procedures being performed.
   - Study procedures that do not affect the patient's safety, eligibility confirmation and response assessment not done.
   - Patient did not answer to all the questions of the MPN-SAF QOL Questionnaire. Information partially collected.

6. Laboratory:
   - Back-up sample of $JAK2^{V617F}$, PK and PD not collected.
   - Primary and back-up samples of $JAK2^{V617F}$, PK and PD of the same patient and collected at the same visit, shipped to the Central Laboratory with the same shipment.
   - PK and/or PD samples not collected at pre-dose at visit Day1 Cycle 1 and at the subsequent time points as predicted by the protocol.
   - Blood samples drawn by staff not listed on study delegation log or site staff not certified.

All potential protocol deviations will be discussed and reviewed on a case-by-case basis before the database lock.

Individual protocol deviations will be presented in a data listing. The number and percentage of patients with protocol deviations will be summarized by deviation. Additional Major and Minor protocol deviations may be identified during data review and will be reflected in the table and listing as appropriate.

5.4. MAXIMUM TOLERATED DOSE ANALYSIS SET (MTD)

The MTD analysis set will include all patients who experienced DLTs in Cycle 1 of **Part A**, or who received at least 90% of the doses of study medication in Cycle 1 of **Part A**. The data regarding the Cycle 1 of **Part A** will be used to determine MTD from this analysis set.

5.5. PK ANALYSIS SET (PK)

The PK Analysis Set will consist of all SAF patients with at least 1 PK assessment.

This analysis set will be used for PK analysis.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

For both **Part A** and **Part B**, reference start date is defined as the day of the first dose of study medication (C1D1 is the day of the first dose of study medication) and is referred to as "Day 1" for the definition of the Baseline value. Day - 1 is the day that precedes Day 1. Day 0 is not defined.

The date and the time of the first investigational study drug of each patient will be taken from the "On-site Dosing (DOSING)" raw data panel.

- *If the date of the event is on or after the reference date then:*
  Study Day = (date of start of the event – reference date) + 1.

- *If the date of the event is prior to the reference date then:*
  Study Day = (date of start event – reference date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day, and any corresponding durations will be presented based on the imputations specified in Appendix 2; Partial Date Conventions.

The duration of an event will be presented in days, rounded to one decimal place and will be calculated as follows:

Duration of event= (date of end of event – date of start of event) + 1.

In the case of a retest (same visit number assigned) of a non laboratory data (i.e. 3 ECG repeated as per QTc prolongation), the average of all measurements will be used for by-visit summaries.

Early termination data will be summarised in the specific visit where occurred.

Listings will include all scheduled, unscheduled and early discontinuation data.

6.2. BASELINE

The Screening/Baseline Period is defined as the period from informed consent signature to the first investigational study drug administration (i.e. C1D1 in **Parts A** and **B**). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline (i.e. C1D1), but Adverse Events (AEs) and medications commencing on the reference start date will be considered post-baseline.

Baseline, is defined as the last scheduled non-missing measurement taken prior to dosing and will correspond to Day 1 (i.e. C1D1 in **Parts A** and **B**) for clinical laboratory evaluations and physical examinations and to Day 1, predose for PK concentrations, PD assessments vital signs and ECGs. However, if a patient is missing the planned baseline collection, the previous non-missing evaluation will become the baseline value.

The Baseline descriptive analysis will be based on the SAF set.

6.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented.

Unscheduled safety measurements (Laboratory, Vital signs, ECG) of all patients, within each dose level for **Part A** and within MTD, for **Part B**, will be evaluated as following:

- if a planned visit was not performed, the nearest (±3 days) unscheduled visit will be considered as the correspondent planned one.
- if unscheduled visits were performed in addition of the planned one, each unscheduled visit between two planned ones will be summarized and ordered by date.

In the case of a retest (same visit number assigned) of a non laboratory data (i.e. 3 ECG repeated as per QTc prolongation), the average of all measurements will be used for by-visit summaries.

Early termination data will be summarised in the specific visit where occurred.

Listings will include all scheduled, unscheduled and early discontinuation data.

6.4. WINDOWING CONVENTIONS

No visit windowing will be performed for this study at this time.

6.5. STATISTICAL TESTS

The main purpose of this phase Ib/II study consists in providing accurate estimates of clinically relevant variables and measures.

The two tailed 95% confidence intervals of the primary endpoint will be computed using the Normal Approximation or exact method (as applicable) for proportions. Confidence intervals for model parameters will be based on either the profile likelihood function. All tests will be two-sided, unless otherwise specified in the description of the analyses.

6.6. COMMON CALCULATIONS

For quantitative measurements, change from baseline (absolute and percentage) will be calculated as:

- Test Value at Visit X – Baseline Value
- (Test Value at Visit X – Baseline Value)/ Baseline Value*100

6.7. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.2 (or higher).

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

No adjustment for covariates will be performed for this study.

7.2. MULTICENTRE STUDIES

This study will be conducted by multiple investigators at multiple centres internationally.

No statistical adjustment will be made for geographic region. Geographic Region or Site related differences will not be evaluated.

7.3. MISSING DATA

Missing data will not be imputed.

Notably, both in Part A and in Part B, in case the patient completes the study (i.e. performs all the evaluations requested to be done at the Day 28 of Cycle 6), the evaluation performed at C6D28 visit can be counted for the End of Study visit.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

No adjustments for type I error inflation due to multiplicity of the tests will be considered.

7.5. EXAMINATION OF SUBGROUPS

Sub-group analyses will be performed for exploratory purposes and are related to the evaluation of: each single parameter of the clinical-haematological ELN response criteria [1] and the "**new**" ELN response criteria (for **Part B** only) [2]; spleen size (by MRI or CT scan) in patients with confirmed splenomegaly at baseline; disease-related quality of life; $JAK2^{V617F}$ allele burden and reduction of the symptomatic treatment of pruritus.

Since these analyses will be used to promote hypotheses rather than confirm them, no adjustments for type I error inflation due to multiplicity of the tests will be considered. Moreover post-hoc and data-driven analyses will be carefully considered and ranked according to their biological plausibility.

8. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the data presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by Quintiles Biostatistics.

Both continuous and categorical data will be summarised and tabulated in 2-way tables (i.e. variable-by-DL, variable-by-visit, visit-DL, etc).

Statistical tables will be presented by treatment DL and the treatment labels to be used in the Tables, Listings and Figures (TLFs) are defined in **Table 1.1**.

The DL will be sorted, so that DL1 appears as first.

All data will be listed sorted by site, patient ID and within patient by visit (*where appropriate*).

The visit names/labels to be used in the analysis data sets and in the TLFs are defined in **Table 3**.

Table 3 – Study Visits performed in *Parts A* and *B*

Study Part	Visit	Visit label for Tables, Listings and Figures (TLFs)[1]
Part A	Screening Visit	A - Baseline
	Cycle 1 Day 1 Visit – PRE-DOSE	A - C1D1 – PRE
	Cycle 1 Day 1 Visit – POST-DOSE	A - C1D1 - POST

	Cycle 1 Day 2 Visit	A - C1D2
	Cycle 1 Day 3 Visit	A - C1D3
	Cycle 1 Day 4 Visit	A - C1D4
	Cycle 1 Day 8 Visit	A - C1D8
	Cycle 1 Day 10 Visit	A - C1D10
	Cycle 1 Day 15 Visit	A - C1D15
	Cycle 1 Day 22 Visit	A - C1D22
	Cycle 1 Day 28 Visit	A - C1D28
	Cycle 2 Day 28 Visit	A - C2D28
	Cycle 3 Day 28 Visit	A - C3D28
	Cycle 4 Day 28 Visit	A - C4D28
	Cycle 5 Day 28 Visit	A - C5D28
	Cycle 6 Day 28 Visit	A - C6D28
	End of Study Visit for completers patients	A – EOS
	Unscheduled Visit n. 1 – PRE-DOSE	A - UNSCHEDULED 1 – PRE*
	Unscheduled Visit n. 2 – PRE-DOSE	A - UNSCHEDULED 1 – PRE*
	…	…
	Unscheduled Visit n. *N* – PRE-DOSE	A - UNSCHEDULED *N* – PRE*
	Unscheduled Visit n. 1 – POST- DOSE	A - UNSCHEDULED 1 – POST*
	Unscheduled Visit n. 2 – POST- DOSE	A - UNSCHEDULED 2 – POST*
	…	…
	Unscheduled Visit n. *N* – POST-DOSE	A - UNSCHEDULED *N* – POST*
Part B	Screening Visit	B - Baseline
	Cycle 1 Day 1 Visit – PRE-DOSE	B - C1D1 – PRE
	Cycle 1 Day 1 Visit – POST-DOSE	B - C1D1 – POST
	Cycle 1 Day 28 Visit	B - C1D28
	Cycle 2 Day 28 Visit	B - C2D28
	Cycle 3 Day 28 Visit	B - C3D28
	Cycle 4 Day 28 Visit	B - C4D28
	Cycle 5 Day 28 Visit	B - C5D28
	Cycle 6 Day 28 Visit	B - C6D28
	End of Study Visit	B - EOS

	Unscheduled Visit n. 1 – PRE-DOSE	B - UNSCHEDULED 1 – PRE*
	Unscheduled Visit n. 2 – PRE-DOSE	B - UNSCHEDULED 1 – PRE*
	…	…
	Unscheduled Visit n. *N* – PRE-DOSE	B - UNSCHEDULED *N* – PRE*
	Unscheduled Visit n. 1 – POST- DOSE	B - UNSCHEDULED 1 – POST*
	Unscheduled Visit n. 2 – POST- DOSE	B - UNSCHEDULED 2 – POST*
	…	…
	Unscheduled Visit n. *N* – POST-DOSE	B - UNSCHEDULED *N* – POST*

[1] In all cases, the day of the visit should be reported.* To be ordered on the basis of the date of the visit.

EOS visit refers to the endpoint value (last non-missing value) for all patients. Notably, both in **Part A** and in **Part B**, in case the patient completes the study (i.e. performs all the evaluations requested to be done at the Day 28 of Cycle 6), the evaluation performed at C6D28 visit can be counted for the End of Study visit.

9. DISPOSITION AND WITHDRAWALS

All patients who provide informed consent will be counted for this Study. Therefore, the number of consented patients by site will be displayed.

Patient disposition and withdrawals, and protocol violations (including inclusion and exclusion criteria), will be presented for the SAF set. Therefore, the number of patients who were recruited, treated and completed the study, as well as the reasons for all discontinuations, grouped by DL, will be presented.

A patient disposition listing with reasons for discontinuation will also be provided.

Drop-out visit refers to patients who prematurely discontinued the treatment showing data recorded during their last assessment visit.

Screening failures will be handled in the analysis for the pertinent data (i.e. screening visit), but they will be reported separately from the treated patients.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the SAF analysis set.

No statistical testing will be carried out for demographic or other baseline characteristics.

Default summary statistics will be produced by treatment group and overall - i.e. for each DL in **Part A** as per **Table 1.1**, for the 12 patients of **Part B** – Stage 1 and for the 28 patients of **Part B** – Stage 2 - for the following demographic and other baseline characteristics reported for this Study:

- Visit date (to be reported only in the patient's data listings).
- Fasting Conditions: Fasting Conditions for at least 8 hours before the time of the visit (Yes/No/Not Applicable).
- Informed Consent Form (ICF): date of ICF signature (to be reported only in the patient's data listings), Yes/No.
- Bone Marrow Histology ICF: date of bone marrow histology ICF signature (to be reported only in the patient's data listings and **only for Part B**), Yes/No/Not Applicable.
- Demography: Date of birth (to be reported only in the patient's data listings), Age (years), Age Group (<60 years/≥60 years), Sex (Female/Male) and Race (White, Asian, Asian Indian, Black, American Indian or Alaska native, Pacific Islander, Other).
- Inclusion and Exclusion Criteria (to be reported only in the patient's data listings).
- Disease History: Date of Initial Diagnosis (years), Time form Diagnosis (months), Type of disease (PV, ET, MF).
- Disease Treatment – Medications: description (to be reported only in the patient's data listings) of previous drug treatments, including medication name (e.g. hydroxyurea, cardioaspirin, etc etc), dose, unit (e.g. mg, g, L, etc etc), frequency (e.g. o.d., b.i.d., t.i.d., q.i.d., other), route of administration (e.g. oral, infusion), treatment start date (years), treatment end date (years), best response to the therapy as per ELN Response criteria (i.e. Complete Response, Partial Response, No Response, Other) [1], reason for discontinuation (Therapy ineffective, Adverse reaction, Other).

  Prior disease medications are defined as those starting and ending prior to the first administration of investigational study drug. Prior medications will be classified according to active drug substance using the WHO-DRL Drug Dictionary (Version 01SEP2017). Frequency tabulations will be presented

for prior medication by primary therapeutic subgroup (3rd level ATC code), generic name, active principle and treatment group.

- Disease Treatment non-drug therapies: description (to be reported only in the patient's data listings) of procedures (i.e. phlebotomy, transfusion, other), Start Date (years), End Date (years), best response to therapy as per ELN Response criteria (i.e. Complete Response, Partial Response, No Response, Other) [1], reason for discontinuation (Therapy ineffective, Adverse reaction, Other). Patients requiring phlebotomy will be produced additionally.

- Medical History: description (to be reported only in the patient's data listings) of Medical History Diagnosis (i.e. disease), Start Date (years), End Date (years), Current Medication (Yes/No).

  Any condition entered on the *Relevant medical history / current medical conditions* CRF will be coded using the MedDRA dictionary (version 20.1). They will be summarised in tables by system organ class (SOC) and preferred term (PT) of the MedDRA dictionary using Safety analysis set. A data listing will be produced for all the patients' medical history. Patients with previous thrombosis history and age ≥60 years and previous thrombosis history will be produced.

- Physical Examination: Physical Examination Performed (Yes/No), Any Clinically Significant Abnormalities Found (Yes/No).

- Vital Signs: date of evaluation (to be reported only in the patient's data listings), Systolic Blood Pressure (mmHg), Diastolic Blood Pressure (mmHg), Heart Rate (bpm), Respiratory Rate (resp/min), Body Temperature (°C), Height (cm), Weight (kg). Controlled hypertension (i.e. Normal ranges for systolic blood pressure: less than 120 mmHg, diastolic blood pressure: less than 80mmHg) at baseline will be produced.

- ECOG: date of evaluation (to be reported only in the patient's data listings), value (i.e. 0, 1, 2, 3, 4, 5).

- Contraception Method:
  - Female of childbearing potential:
    - True abstinence (absence of any sexual intercourse);
    - Double barrier contraception such as diaphragm or a barrier method of contraception in conjunction with spermicidal jelly;
    - Intra-uterine device (non-hormone-releasing) in place for at least 90 days previously and the male partner must use a condom with spermicide;
    - Tubal ligation at least 6 months previously and 1 additional acceptable contraception method;
    - Vasectomy of the male partner (with negative sperm post-vasectomy semen analysis) at least 6 months previously and 1 additional acceptable contraception method;
  - Female of non-childbearing potential:

- Postmenopausal;
- Documented hysterectomy and/or oophorectomy;

o Male :
- True abstinence (absence of any sexual intercourse);
- Condom with spermicide and female partner must use an acceptable method of contraception;
- Vasectomy of the male partner (with negative sperm post-vasectomy semen analysis) at least 6 months previously and 1 additional acceptable contraception method;
- No participation in sperm donation.

– Pregnancy: Date of test, Result (Positive/Negative), Sample taken (Urine/Serum), Reason to not done (to be reported only in the patient's data listings).

Notably, the pregnancy test (*if indicated*) are performed within 72 hours before the first Givinostat dose. The test can be performed by urine or serum pregnancy test. In case of a borderline-positive urine pregnancy test, this is confirmed with a serum pregnancy test and the result recorded in the electronic CRF. These data will presented.

– Blood Chemistry: Sample Date (to be reported only in the patient's data listings), Laboratory ID (to be reported only in the patient's data listings), value, unit (as per International Units), interpretation (Normal/Abnormal and Not clinically significant/Abnormal and Clinically Significant) of the following parameters:

o Sodium;
o Potassium;
o Calcium;
o Chloride;
o Magnesium;
o Albumin;
o Glucose;
o Blood Urea Nitrogen (BUN);
o Urea;
o Creatinine;
o Alanine Aminotransferase (ALT);
o Aspartate Aminotransferase (AST);
o Alkaline Phosphatase;
o Total Bilirubin;
o Lactate Dehydrogenase;
o eGFR (as per Mayo Clinic Quadratic Equation).

– Urinalysis: Sample Date (to be reported only in the patient's data listings), Laboratory ID (to be reported only in the patient's data listings), value, unit (as per International Units), interpretation

(Normal/Abnormal and Not clinically significant/Abnormal and Clinically Significant) of the following parameters:

- pH;
- Specific Gravity;
- Glucose;
- Protein.

– Haematology: Sample Date (to be reported only in the patient's data listings), Laboratory ID (to be reported only in the patient's data listings), value, unit (as per International Units), interpretation (Normal/Abnormal and Not clinically significant/Abnormal and Clinically Significant) of the following parameters:

- Haematocrit (HCT);
- Haemoglobin (Hb);
- RBC;
- PLT;
- WBC;
- Basophils;
- Eosinophils;
- Lymphocytes;
- Monocytes;
- Neutrophils;
- Mean Corpuscular Volume (MCV);
- Mean Corpuscular Haemoglobin (MCH);
- Mean Corpuscular Haemoglobin Concentration (MCHC).

– ECG: Evaluation Date (to be reported only in the patient's data listings), value of the following parameters:

- RR Interval (sec);
- QT interval (msec);
- QTc interval as per Bazzet's correction formula (msec).

Results Interpretation (Normal/Abnormal and Not clinically significant/Abnormal and Clinically Significant), Findings detected in the ECG evaluation – that will be presented by primary SOC and Preferred Term using the MedDRA dictionary (version 20.1) – and related Interpretation (Normal/Abnormal and Not clinically significant/Abnormal and Clinically Significant).

If the first ECG evaluation demonstrated a prolonged QTc interval (i.e. a QTc interval ≥ 450 msec), two additional ECG evaluations over a brief period of time (i.e. 5 minutes between each recording) are performed. The averaged value of these three ECG evaluations is used for the evaluation of the QTc interval requested by the exclusion criterion n. 3. In the electronic CRF all the performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*.

In the patient listings all the additional ECG data have to be presented as soon as the first one.

- Spleen: Evaluation Date (to be reported only in the patient's data listings), Imaging Technique (i.e. MRI, CT scan), Results Interpretation (Normal/Abnormal and Not clinically significant/Abnormal and Clinically Significant) and value of the following parameters:
  - Longitudinal Diameter (cm);
  - Antero-Posterior Diameter (cm);
  - Transversal Diameter (cm);
  - Splenic Volume Index (SVI, in cm^3).

  Notably, patients with splenomegaly performed the spleen evaluation as per site-specific clinical practice. Therefore, patients with splenomegaly before the treatment start are followed according to institutional guidelines (i.e. MRI, CT scan). The same imaging technique and the same instrument is used on a patient throughout the Study, *when possible*. No spleen evaluation is performed in splenectomised patients.

- Molecular Examination: Sample Collection Date (to be reported only in the patient's data listings), Sample Accession Number (to be reported only in the patient's data listings), Back-Up Sample Collection Date (to be reported only in the patient's data listings), Back-Up Sample Accession Number (to be reported only in the patient's data listings) and value of the following parameters:
  - Positivity (Yes/No);
  - Qualitative Evaluation (Homozygous/Heterozygous);
  - Quantitative Evaluation (%).
- MPN-SAF Quality of Life Questionnaire: Completion Date (to be reported only in the patient's data listings) and value (from a score 0 to a score 10) of the following parameters:
  - Level of fatigue right NOW (i.e. at the completion of the MPN-SAF questionnaire);
  - USUAL level of fatigue during past 24 hours (i.e. 24 hours before the completion of the MPN-SAF questionnaire);
  - WORST level of fatigue during past 24 hours (i.e. 24 hours before the completion of the MPN-SAF questionnaire);
  - Fatigue has interfered with General Activity during the past 24 hours (i.e. 24 hours before the completion of the MPN-SAF questionnaire);
  - Fatigue has interfered with Mood during the past 24 hours (i.e. 24 hours before the completion of the MPN-SAF questionnaire);
  - Fatigue has interfered with Walking Ability during the past 24 hours (i.e. 24 hours before the completion of the MPN-SAF questionnaire);
  - Fatigue has interfered with Normal Work (includes work both outside the home and daily chores) during the past 24 hours (i.e. 24 hours before the completion of the MPN-SAF questionnaire);

- Fatigue has interfered with Relations with other people (includes work both outside the home and daily chores) during the past 24 hours (i.e. 24 hours before the completion of the MPN-SAF questionnaire);
- Fatigue has interfered with Enjoyment of life (includes work both outside the home and daily chores) during the past 24 hours (i.e. 24 hours before the completion of the MPN-SAF questionnaire);
- Patient's difficulty with Filling up quickly when eats (early satiety) during the past week (i.e. one week before the completion of the MPN-SAF questionnaire);
- Patient's difficulty with Abdominal pain during the past week (i.e. one week before the completion of the MPN-SAF questionnaire);
- Patient's difficulty with Abdominal discomfort during the past week (i.e. one week before the completion of the MPN-SAF questionnaire);
- Patient's difficulty with Inactivity during the past week (i.e. one week before the completion of the MPN-SAF questionnaire);
- Patient's difficulty with Problems with Headaches during the past week (i.e. one week before the completion of the MPN-SAF questionnaire);
- Patient's difficulty with Problems with Concentration during the past week (i.e. one week before the completion of the MPN-SAF questionnaire);
- Patient's difficulty with Dizziness/ Vertigo/ Light-headedness during the past week (i.e. one week before the completion of the MPN-SAF questionnaire);
- Patient's difficulty with Numbness/ Tingling (in hands and feet) during the past week (i.e. one week before the completion of the MPN-SAF questionnaire);
- Patient's difficulty with Difficulty sleeping during the past week (i.e. one week before the completion of the MPN-SAF questionnaire);
- Patient's difficulty with Depression or sad mood during the past week (i.e. one week before the completion of the MPN-SAF questionnaire);
- Patient's difficulty with Problems with Sexual Desire or Function during the past week (i.e. one week before the completion of the MPN-SAF questionnaire);
- Patient's difficulty with Cough during the past week (i.e. one week before the completion of the MPN-SAF questionnaire);
- Patient's difficulty with Night Sweats during the past week (i.e. one week before the completion of the MPN-SAF questionnaire);
- Patient's difficulty with Itching (pruritus) during the past week (i.e. one week before the completion of the MPN-SAF questionnaire);
- Patient's difficulty with Bone Pain (diffuse not joint pain or arthritis) during the past week (i.e. one week before the completion of the MPN-SAF questionnaire);
- Patient's difficulty with Fever during the past week (i.e. one week before the completion of the MPN-SAF questionnaire);
- Unintentional weight loss last 6 months (i.e. six months before the completion of the MPN-SAF questionnaire);
- Overall Quality of Life statement;

- MPN-SAF Total Symptom Score (TSS) (**only for Part B**).
- Number of patients with Pruritus, Headache, Microvascular Symptoms

– Bone Marrow (**only for Part B**): Evaluation Date (to be reported only in the patient's data listings) and the following parameters:
  - Is age-adjusted normocellularity present? (Yes/No);
  - Is trilinear hyperplasia absent? (Yes/No);
  - Is there an absence of grade >1 reticulin fibrosis? (Yes/No).

– ENROLL: Date of Enrolment Request (to be reported only in the patient's data listings), Study Part (Part A/Part B), Enrolment Confirmation Date (to be reported only in the patient's data listings), Dose Level (DL1, DL1 – expanded, DL6, DL0), Patient ID.

Listings of patient's baseline characteristics will be produced on all consented patients.

10.1. DERIVATIONS

- Age (years) = Date of Signature of Informed Consent – Date of Birth

Notably, due to privacy law applicable in some countries included in this Study (e.g. Italy), in the electronic CRF only the months and the year of birth were collected. Therefore, since the day of birth was not collected on electronic CRF, this will be defined as the first day of the month of birth.

- Time form Diagnosis (months) = Date of Signature of Informed Consent - Date of Initial Diagnosis

11. MEDICAL HISTORY

Medical History information will be presented for the SAF analysis set.

- Medical History will be coded using version 20.1 of Medical Dictionary for Regulatory Activities (MedDRA) dictionary.
- Medical History conditions are defined as those conditions recorded on eCRF form "MH".
- Presented by System Organ Class (SOC) and Preferred term (PT).

12. PRIOR AND CONCOMITANT ILLNESSES

Prior and Concomitant Illnesses will be presented for the SAF analysis set.

- Prior and Concomitant Illnesses will be coded using the version 20.1 of MedDRA dictionary.
- Prior disease medications are defined as those starting and ending prior to the first administration of investigational study drug.
- Concomitant Illnesses are conditions recorded on eCRF form “MH” and which started prior to or at Screening and are ongoing at the date of Screening.
- Presented by SOC and PT.

12.1. POST-TREATMENT DISEASES

Post-treatment disease will be presented for the SAF analysis set.

- Post-treatment diseases will be coded using the version 20.1 of MedDRA Dictionary.
- Post-treatment diseases are conditions recorded on electronic CRF in the Form “AE” and which started after the last Study drug intake.
- Presented by SOC and PT.

13. MEDICATIONS (I.E. DRUGS)

Prior medications to treat PV will include regimens discontinued up to 24 weeks prior to enrolment. The information captured in electronic CRF included drug name, start and stop dates, best response to therapy (*where applicable*) and reason for discontinuations.

Medications will be presented for the SAF analysis set and coded using the 01SEP2017 version of WHO-DRL Dictionary. Frequency tabulations will be presented for prior and concomitant medication by primary therapeutic subgroup (3rd level ATC code), generic name and active principle.

See Appendix 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior, concomitant, or post treatment, the medication will be classified by the worst case (i.e. concomitant medication):

- ‘Prior’ drug medications are defined as those starting and ending prior to the first administration of investigational Study drug (i.e. C1D1).

- 'Concomitant' drug medications are defined as those started at or after first administration of Study drug (i.e. C1D1) and include those started prior to the first administration of investigational Study drug (i.e. C1D1) but continued during the Study.

- 'Post' drug medications are defined as drug medications which started after the last Study drug intake.

13.1. NON-DRUGS THERAPIES

Prior and significant non-drug therapies (e.g. phlebotomies, transfusions) to treat PV will include regimens discontinued up to 24 weeks prior to enrolment. Non-drug-therapies will be summarised by type of procedure (i.e. transfusion, phlebotomy, other), date of procedure, reason for procedure. Non-drug therapies (e.g. transfusion, phlebotomy) will be presented for the SAF analysis set.

See Appendix 2 for handling of partial dates for non-drugs therapies, in the case where it is not possible to define a non-drug therapy as prior, concomitant, or post treatment, the non-drug therapy will be classified by the worst case (i.e. concomitant non-drug therapy):

- 'Prior' non-drug therapies are defined as those starting and ending prior to the first administration of investigational Study drug (i.e. C1D1).

- 'Concomitant' non-drug therapies are defined as those started at or after first administration of Study drug (i.e. C1D1) and include those started prior to the first administration of investigational Study drug (i.e. C1D1) but continued during the Study.

- 'Post' non-drug therapies are non-drug therapies which started after the last Study drug intake.

Frequency tabulations will be also presented for significant non-drug therapies.

Notably, all phlebotomies performed in the first 3 weeks of treatment will be not counted to assess the clinico-haematological response according to the clinico-haematological ELN response criteria [1] at C3D28 and at C3D28 in **Parts A** and **B**.

14. STUDY MEDICATION EXPOSURE

Exposure to study medication in days will be presented for the SAF analysis set.

The date of the first investigational study drug of each patient will be taken from the

"On-site Dosing (DOSING)" raw data panel. This date of first investigational study drug administration

(Day 1) is the key variable RFSTDTN and used in the calculation of relative days.

The date of first study medication administration will be taken from the eCRF "Dosing" Form (C1D1).

The date of the last investigational study drug of each patient will be taken from the "Patient Disposition" form of eCRF. If the date is missing, the date of the last visit will be imputed, if appropriate. This date of last investigational study drug is the key variable RFENDTN.

The duration (days) of exposure and the daily dosage (mg) of Givinostat will be calculated for each patient, and will be summarized descriptively including the mean, standard deviation, median, minimum and maximum.

A listing of treatment exposure data, including the first and last dates of Study drug administration will be presented by-subject and within-subject by available interval and overall exposure.

Interruptions, compliance, and dose changes are not taken into account for duration of exposure.

Reason for treatment discontinuation and number of patients treated beyond protocol-specified discontinuation criteria will also be summarised. Analysis will be based on safety population.

In general, In the case of missing data on the eCRF, the cycle C1D1 visit date and the last visit cycle performed date will be used in order to determine the first and last date of study medication.

14.1. DERIVATIONS

The duration of investigational study drug or exposure to treatment is equal to the day number of the last day of drug administration (LDA) and is derived as follows from the previous two dates (RFSTDTN and RFENDTN):

LDA (days) = (Date of Last Drug Administration [RFENDTN] – Date of First Drug Administration [RFSTDTN]) + 1

LDA then indicates the relative day that the last dose of investigational study drug is administered per patient, as calculated relative to the first day of dosing.

15. STUDY MEDICATION COMPLIANCE

The Investigator recorded in the electronic CRF the assigned dose of Givinostat and any dose reduction (*if applicable*) to allow the evaluation of compliance to treatment. At each visit, patients brought back to the Study site all drug bottles previously received (i.e. used, partially used and unused) and receive a new Study drug supply. The number of residual capsules in the dispensed bottles were counted by the Investigator and reported in the electronic CRF.

Compliance with Givinostat treatment will be calculated based on the Study drug accountability documented by the site staff and monitored by Italfarmaco S.p.A. or its designee (i.e. capsule counts).

A patient will be considered sufficiently compliant with Givinostat treatment if he/she has taken at least 80% of the prescribed dose over the total duration of Study drug dosing. In addition, patients who didn't experience a DLT and missed more than 10% of the doses in Cycle 1 of **Part A** will be considered not sufficiently compliant.

Treatment compliance to Study drug will be presented for the SAF analysis set, ITT analysis set, PP analysis set, MTD analysis set and PK analysis set, during all six Cycles of treatment (i.e. from C1D1 to C6D28). Treatment compliance will be calculated for C1D1 – C1D28 in ***Part A***, and C1D1 – C6D28 in **Parts A** and **B** (both Stages).

Treatment compliance per interval is defined as the number of capsules that were actually taken within a given interval relative to the number of capsules that should have been taken by the patient for the duration of actual treatment exposure for that interval.

Summary statistics for the Actual Total Dose delivered (mg), Givinostat Dose Intensity (mg/day) will be presented.

Summaries showing Givinostat dose modification during the Study will be presented by treatment group.

15.1. DERIVATIONS

In general, the percentage compliance (%), assessed by capsule count, will be calculated as follows:

- "Per visit" Compliance to study medication will be calculated as follows:

$$\frac{\{([\text{N of Capsules dispensed at Visit } (n)] - [\text{N of Capsules returned at Visit } (n+1)])}{[[\text{Date of Visit } (n+1)] - [\text{Date of Visit } (n)]]\text{x Number of capsules prescribed by day}} \quad \text{x 100}$$

- Overall Compliance to study medication will be calculated as follows:

$$\frac{\begin{array}{c}\{([\text{N of Capsules dispensed at Cycle 1}] - [\text{N of Capsules returned at Cycle 2}]) \\ + \cdots + \\ ([\text{N of Capsules dispensed at Cycle}(n-1)] - [\text{N of Capsules returned at Cycle}(n)])\}\end{array}}{[[\text{Date of Cycle}(n)] - [\text{Date of Dispensing at Cycle 1}]+1\,]\text{x Number of capsules prescribed by day}} \quad \text{x 100}$$

Also for the last cycle compliance calculation this formula will be used as the last dose of study drug date considering from disposition page.

For patients who permanently stop the study medication, the "Date of visit (n)" will be replaced by the date of study withdrawal.

A patient will be considered sufficiently compliant with Givinostat treatment if he/she has taken at least 80% of the prescribed dose over the total duration of study drug dosing.

The calculated percentage compliance per interval will be categorized as:

A) ***Part A*** – Cycle 1:
   - Too Low: ≤ 90% compliance.
   - Adequate: > 90% to ≤ 100% compliance.
   - Too High: > 100% compliance.

B) ***Part A*** (all Cycles) and ***Part B***:
   - Too Low: < 80% compliance.
   - Adequate: ≥ 80% to ≤ 100% compliance.
   - Too High: > 100% compliance.

Categories of overall compliance will be presented by treatment group using default summary statistics. Calculated compliance (%) per applicable interval and overall will be also presented.

All drug accountability data will be presented, that is, the number of capsules dispensed and returned at each applicable interval. The total number of capsules taken per applicable interval and overall (%), as well as the calculated compliance (%) per applicable interval and overall will be presented, *if applicable*.

The Givinostat summary statistics for the Actual Total Dose delivered (mg) and Dose Intensity Givinostat: DI (mg/day) will be presented and calculated as follow:

Actual Total Dose delivered (mg) = sum over all days of actual dose received (mg).

Dose Intensity Givinostat: DI (mg/day) = [Actual Total Dose Level of Givinostat (mg)/Duration of exposure (days)].

16. EFFICACY AND SAFETY VARIABLES

16.1. DEFINITION OF END OF THE STUDY

The end of the Study (last patient last visit) will occur after all patients in whole Study (**Part B**) have completed their last assessment as per Study protocol. Note that the analysis of the biological samples could be performed after the end of Study due to scientific (i.e. after evaluation of preliminary results and data exploration, some additional analyses could be performed to identify and quantify other molecular parameters of interest in term of improving of the knowledge of cMPN and the activity of the drug in these disorders) or technical reason.

In any case, after the completion of the analysis all data should be formally reported in a Clinical Study Report and/or in a specific technical report.

16.2. EFFICACY ASSESSMENT

Timing information are summarised in the Study flow-chart (Appendix A of the Study protocol) and detailed in the paragraph 4.5.4 of the Study protocol.

16.3. CRITERIA FOR ASSESSING CLINICO-HAEMATOLOGICAL IMPROVEMENT

Disease response will be evaluated according to the following clinico-haematological ELN criteria [1] after 3 and 6 cycles (i.e. at weeks 12 and 24, respectively) of treatment with Givinostat both in ***Part A*** (exploratory endpoints) and in ***Part B*** (primary and secondary endpoints, respectively).

- ***Complete response***:
  1. HCT < 45% without phlebotomy, **and**
  2. Platelets ≤ 400 x 10^9/L, **and**
  3. WBC ≤ 10 x10^9/L, **and**
  4. Normal spleen size, **and**
  5. No disease-related systemic symptoms (i.e. pruritus, headache, microvascular disturbances).

- ***Partial response:***
  Patients who do not fulfil the criteria for complete response and
  1. HCT < 45% without phlebotomy, **or**
  2. Response in 3 or more of the other criteria.

- ***No response***: any response that does not satisfy partial response.

Only in case the enrolment in ***Part A*** is slow (i.e. **< 5 patients enrolled in 3 months**) and the eligibility for this part of the study may be expanded to all patients with cMPN, disease response for this part of the study can be evaluated according to the clinico-haematological ELN and EUMNET criteria [7] after 3 and 6 cycles of treatment with Givinostat, in ET and MF patients, respectively.

For ET (from the clinico-haematological ELN response criteria):

- ***Complete response:***
  1. Platelets ≤ 400 x10^9/L, **and**
  2. No disease related systemic symptoms (i.e. pruritus, headache, microvascular disturbances), **and**
  3. Normal spleen size, **and**
  4. WBC ≤10 x10^9/L.

- ***Partial response:***

  Patients who do not fulfil the criteria for complete response and
  1. Platelet count < 600 x 10^9/L, **or**
  2. Platelet count decrease > 50% from baseline.

- ***No response***: any response that does not satisfy partial response.

Both for PV and ET patients, all phlebotomies performed in the first 3 weeks of treatment are **not** counted to assess the clinico-haematological response.

For MF (from EUMNET response criteria)

- ***Complete response:*** complete response in anemia, splenomegaly, constitutional symptoms, platelet and leukocyte count.
  1. *Complete response in anaemia:* Haemoglobin ≥ 12 g/dL for transfusion-independent patients or ≥ 11 g/dL for transfusion-dependent patients (applicable only for patients with baseline haemoglobin level of < 10 g/dL);
  2. *Complete response in splenomegaly:* Spleen not palpable;
  3. *Complete response in constitutional symptoms:* Absence of constitutional symptoms (fever, drenching night sweats, or ≥ 10% weight loss);
  4. *Complete response in platelet count:* Platelet count 150-400 x10^9/L;
  5. *Complete response in leukocyte count:* Leukocyte count 4-10 x10^9/L.

- ***Major response:*** Any response in both anaemia and splenomegaly without progression in constitutional symptoms **or** complete response in anaemia without progression in splenomegaly **or** partial response in anaemia in a baseline transfusion-dependent patient combined with response in constitutional symptoms without progression in splenomegaly **or** any response in splenomegaly combined with response in constitutional symptoms without progression in anaemia.
  1. *Partial response in splenomegaly: Either ≥ 50% decrease in spleen size if baseline ≤ 10 cm from left costal margin (LCM) or ≥ 30% decrease if baseline > 10 cm from LCM.*
  2. *Partial response in platelet count: A ≥ 50% decrease in platelet count if baseline > 800 x109/L or platelet count increase by ≥ 50% x 109/L if baseline < 100 x109/L.*
  3. *Partial response in leukocyte count:* A ≥ 50% decrease in leukocyte count of baseline > 20 $x10^9$/L or leukocyte count increase by ≥ 1 $x10^9$/L if baseline < 4 $x10^9$/L
  4. *Progression in anaemia:* A haemoglobin decrease of ≥ 2 g/dL **or** a 50% increase in transfusion requirement **or** becoming transfusion dependent
  5. *Progression in splenomegaly:* A ≥ 50% increase in spleen size if baseline ≤ 10 cm from LCM **or** a ≥ 30% increase if baseline > 10 cm from LCM.
  6. *Progression in constitutional symptoms:* Appearance of constitutional symptoms.

- ***Moderate response:*** Complete response in anaemia with progression in splenomegaly **or** partial response in anaemia without progression in splenomegaly **or** any response in splenomegaly without progression in anaemia and constitutional symptoms.

- ***Minor response:*** Any leukocyte- **or** platelet-based response without progression in anaemia, splenomegaly, **or** constitutional symptoms.

- ***No response:*** Any response that does not qualify at least as minor response.

In all cases (PV, ET and MF patients), the disease-related systemic symptoms are evaluated directly by patients according to MPN-SAF QOL questionnaire [8, 9].

In all cases, the response status of the patient can be reviewed by a panel of independent Investigators, *if necessary*.

In all cases, the medical judgment of the Investigator's is taken into account. In particular, if the Investigator's clinical response assessment – that takes into account the overall medical judgment of the specific patient's case - is not in agreement with the exact application of the clinico-haematological ELN or EUMNET response criteria , the Investigator's assessment will supersede the "mathematical"

application of these criteria and used for analysis into study report. Also mathematical application of ELN response criteria (not agreed by the medical site team) will be analyzed.

16.4. CRITERIA FOR DETERMINATION OF MTD

Once all patients enrolled in **Part A** are treated for at least 1 cycle, the study team (see paragraph 3.2.2.1) determined the MTD to be used in **Part B** based on the safety and tolerability profile of Givinostat observed as well as the PK and PD data, *if applicable*.

16.5. CRITERIA FOR CHARACTERIZATION OF PK

Plasma concentrations from ***Parts A*** and ***B*** are evaluated by dose and time point for all patients and time points with at least one PK assessment.

16.6. THE EFFICACY POPULATION

The analysis sets are defined in the section 5.

Patients with a disease-related global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported in the electronic CRF as disease progression clinically assessed. Every effort should be made to document the objective progression even after discontinuation of treatment.

The response status of the patient may be reviewed by a panel of independent investigators, *if necessary*.

16.7. SAFETY ASSESSMENTS

Safety and tolerability are evaluated by monitoring haematology and blood chemistry, urinalysis (only in the first cycle of ***Part A***), by measurement of physical examination, vital signs, weight, body temperature, ECOG performance status, ECG assessment and evaluation, QTc determination and adverse events recording at scheduled times as described above. Timing information are summarised in the Study flow-chart (Appendix A of the Study protocol) and detailed in the paragraph 4.5.4 of the

Study protocol.

All significant findings already present during the screening visit before drug administration are reported in the appropriate section of electronic CRF, i.e. Medical History section or Current Medical Conditions section. Significant findings occurring after patient enrolment - identified as AEs - are recorded in Adverse Event section of electronic CRF.

The following criteria are used to assess the safety and tolerability both in **Part A** (primary endpoint) and after 3 and 6 cycles (primary and secondary endpoints, respectively) in **Part B**:

- Number of patients experiencing AEs.
- Type, incidence, and severity of treatment-related adverse events, graded according to Common Terminology Criteria for Adverse Events (CTCAE v. 4.03, 14th June 2010).

16.8. LABORATORY EVALUATIONS

The following laboratory examinations (haematology, blood chemistry and urinalysis) are performed at each investigational unit by a local laboratory co-operating with the Investigator following its own procedures:

- **Haematology:** RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- **Blood chemistry:** ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN or Urea (as per site-specific clinical practice), glucose, Na, K, Ca, Cl, Mg, albumin, eGFR determination (according to the Mayo Clinic Quadratic Equation);
- **Urinalysis:** pH, specific gravity, protein, glucose.

The required amount of blood and urine are collected at each visit as scheduled above. Timing information are summarised in the Study flow-chart (Appendix A of the Study protocol) and detailed in the paragraph 4.5.4 of the Study protocol.

All results of laboratory examinations are entered into the appropriate electronic CRF sections.

16.9. CLINICAL SAFETY ASSESSMENTS

Clinical safety assessments include a thorough physical examination, vital signs assessment

(respiratory rate, pulse rate and sitting blood pressure are measured after 5 minutes of rest), weight, body temperature, ECOG performance status, ECG assessment and evaluation, QTc determination (according to Bazett's correction formula, Appendix D of the Study protocol).

Of note, if the ECG evaluation demonstrate a prolonged QTc interval (i.e. a QTc interval ≥ 450 msec), two additional ECG evaluations over a brief period of time (i.e. 5 minutes between each recording) are performed. The averaged value of these three ECG evaluations are used for the evaluation of the QTc interval of the related visit. In the electronic CRF all the performed ECG evaluations are entered as well as the average value of multiple ECG evaluation, *if necessary*.

16.10. ADVERSE EVENTS

All AEs either observed by the Investigator, or reported by the patient spontaneously or in a response to a direct question are evaluated by the Investigator and are recorded on the AE section of the electronic CRF.

If the patient discontinues for any reason (including discontinuation for pregnancy), with drug related adverse event ongoing at Study end, he/she will be followed until resolution or stabilization of the event or until it will be reasonable to consider the event not drug related any more or until the start of a new treatment, whichever occurs first.

In case of multiple reasons (e.g. patient withdraws the consent for toxicity), "adverse event" is indicated as the primary reason whenever applicable. All relevant information related to the reason for treatment discontinuation including contributory factors are included on the electronic CRF.

A complete end of Study visit must be performed by 7 days after the last drug intake for any patient permanently discontinuing Study treatment. All drug-related AEs that are still ongoing beyond the last scheduled visit, are followed at subsequent follow-up visits until recovery. If a patient does not return for a scheduled visit, every effort will be made to contact the patient. In any circumstance every effort will be made to complete and report the observations as thoroughly as possible. All relevant information related to the reason for treatment discontinuation including contributory factors are included on the electronic CRF.

For AEs definitions, coding and reporting procedures see paragraph 5 of the Study protocol.

16.11. EXPLORATORY PARAMETERS

EVALUATION OF THE EFFECTS OF GIVINOSTAT ON EACH SINGLE PARAMETER OF THE CLINICO-HAEMATOLOGICAL ELN RESPONSE CRITERIA

Each single parameter of the clinico-haematological ELN response criteria [1] (see paragraph 16.3) is used to evaluate the effect of Givinostat in PV patients.

Only in case the enrolment in **Part A** is slow (i.e. < 5 patients enrolled in 3 months) and the eligibility for this part of the study may be expanded to all patients with cMPN, in this part of the study each single parameter of the ELN and EUMNET criteria can be used to evaluate the effect of Givinostat in ET and MF patients, respectively.

EVALUATION OF THE EFFECTS OF GIVINOSTAT ON PD MARKERS

To evaluate the effects of Givinostat on PD markers, the analysis on mRNA is used.

After evaluation of preliminary results and data exploration, some additional analyses can be performed to identify and quantify other molecular parameters of interest in terms of improving of knowledge of cMPN and the activity of the drug in these disorders.

SPLEEN SIZE ASSESSMENT

The spleen evaluation is performed at the study centre according to the visit schedule outlined in the flow-chart (Appendix A of the Study protocol).

To evaluate the effects of Givinostat on spleen size, MRI or CT scan is used.

The spleen evaluation is performed during the study according to institutional guidelines and site-specific clinical practice (i.e. MRI or CT scan). For this reason, it is strictly recommended to the sites to provide the Sponsor or their designee with the local normal spleen values of the imaging performed for each patient according to institutional guidelines and site-specific clinical practice (i.e. MRI or CT scan).

The same imaging technique and the same instrument to assess spleen dimension (i.e. MRI or CT scan) is used on a patient throughout the study, *if possible*.

If possible, the spleen dimensions are evaluated as longitudinal diameter (A), antero-posterior diameter (B), transversal diameter (C) and Splenic Volumetric Index (SVI):

$$\mathbf{SVI = (A \times B \times C) / 27}$$

IMPROVEMENT OF CONSTITUTIONAL SYMPTOMS

To evaluate the improvement of disease-related constitutional symptoms, the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) questionnaire (about 20 items) is used in **Parts A and B**, in order to assess the most important clinical symptoms among patients with MPNs [8].

In addition, starting from MPN-SAF questionnaire, in **Part B** also the MPN-SAF Total Symptom Score [9] is assessed as requested by the "new" ELN criteria (i.e. revised ELN response criteria) [2].

REDUCTION OF THE JAK2^{V617F} ALLELE BURDEN

To evaluate the reduction of the JAK2^{V617F} allele burden, the qRT-PCR is used. This molecular examination is performed in a central laboratory (Appendix E of the Study protocol).

After evaluation of preliminary results and data exploration, some additional analyses can be performed to identify and quantify other molecular parameters of interest in terms of improving of knowledge of cMPN and the activity of the drug in these disorders.

REDUCTION OF THE SYMPTOMATIC TREATMENT OF PRURITUS IN TERM OF DOSAGE AND/OR DAYS OF TREATMENT

To evaluate the reduction of the symptomatic treatment of pruritus, the dosage and/or the days of treatment of each concomitant medication taken by the patient to treat this symptom is used. This assessment is performed using the data entered by Investigators in the specific section of the electronic CRF.

EVALUATION OF PRELIMINARY EFFICACY ACCORDING TO THE REVISED ELN CRITERIA

Disease response is evaluated also according to the following "new" ELN criteria (i.e. the revised ELN response criteria) after 6 cycles of treatment with Givinostat in **Part B** [2].

- ***Complete remission***:
  1. *Durable* resolution of disease-related signs including palpable hepato-splenomegaly improvement, and *large symptoms improvement*, **and**
  2. *Durable* peripheral blood count remission, defined as HCT < 45% without phlebotomies, and PLT count ≤ 400 x10^9/L, and WBC count < 10 x10^9/L, **and**
  3. No progressive disease, and absence of any haemorrhagic or thrombotic event, **and**
  4. Bone marrow histological remission defined as the presence of age-adjusted normo-cellularity, and disappearance of tri-linear hyperplasia, and absence of grade > 1 reticulin fibrosis.
- ***Partial remission:***
  1. *Durable* resolution of disease-related signs including palpable hepato-splenomegaly, and *large symptoms improvement*, **and**
  2. *Durable* peripheral blood count remission, defined as HCT < 45% without phlebotomies, and PLT count ≤ 400 x10^9/L, and WBC count < 10 x10^9/L, **and**
  3. No progressive disease, and absence of any haemorrhagic or thrombotic event, **and**
  4. No bone marrow histological remission defined as persistence of tri-linear hyperplasia.
- ***No response***: any response that does not satisfy partial remission.
- ***Progressive Disease***: transformation into post-PV myelofibrosis, myelodysplastic syndrome or acute leukemia (according to the IWG-MRT criteria for the diagnosis of post-PV myelofibrosis and according to WHO criteria for the diagnosis of myelodysplastic syndrome and acute leukemia).

Please note that according to the "new" ELN criteria (i.e. revised ELN response criteria) [2]:

1) Molecular response is not required for assignment as Complete Remission or Partial Remission. Molecular response evaluation requires analysis in peripheral blood granulocytes. Complete response is defined as eradication of a pre-existing abnormality. Partial response applies only to patients with at least 20% mutant allele burden at baseline. Partial response is defined as ≥ 50% decrease in allele burden.
2) *"Durable"* is defined as lasting at least 12 weeks.
3) "*Large symptom improvement*" is defined as ≥ 10 points of decrease in MPN-SAF Total Symptom Score [9].

In all cases, the medical judgment of the Investigator's is taken into account. In particular, if the Investigator's clinical response assessment – that takes into account the overall medical judgment of the specific patient's case - is not in agreement with the exact application of the revised clinico-haematological ELN response criteria , the Investigator's assessment will supersede the "mathematical"

application of these criteria and used for analysis into study report. Also mathematical application of ELN response criteria (not agreed by the medical site team) will be analyzed.

EVALUATION OF THE EFFECTS OF GIVINOSTAT ON EACH SINGLE PARAMETER OF THE REVISED ELN RESPONSE CRITERIA

Each single parameter of the "new" ELN criteria (i.e. revised ELN response criteria) [2] (see section 16.11.7.) is used to evaluate the effect of Givinostat in PV patients in ***Part B***.

17. PRIMARY OUTCOMES

17.1. PART A

The Primary objective of the **Part A** is to characterize the safety, tolerability and MTD of Givinostat in patients with PV. The determination of the MTD of Givinostat will be based on C1 DLTs.

The following primary safety parameters will be evaluated in **Part A** based on SAF analysis set:

- Number of patients experiencing adverse events.
- Type, incidence, and severity of treatment-related adverse events, graded according to Common Terminology Criteria for Adverse Events (CTCAE v. 4.03, 14th June 2010).

AEs will be coded using MedDRA dictionary (using the 20.1 version). AEs will be reported on a per patient basis. If a patient has more than one AE for a treatment that coded to the same PT, the patient will be counted only once for that PT. Similarly, if a patient has more than one AE for a treatment within a SOC category, the patient will be counted only once in that SOC category. A patient with multiple CTCAE grades for an AE will be summarised under the maximum CTCAE grade recorded for the event.

Any AE which started at or after the first administration of Study treatment (i.e. C1D1) will be considered a Treatment Emergent Adverse Event (TEAE). If the start date is missing for an AE, the AE will be considered to be a TEAE.

An overview of AEs including the number of patients with at least one AE, at least one TEAE, at least one drug-related TEAE, at least one Serious TEAE (TESAE), any SAE, any AE leading to death, any TEAE leading to death, any TEAE leading to drug discontinuation, at least one grade ≥ 3 TEAE, will be presented. The following AE frequency tables will be also provided:

- Incidence of TEAEs by primary SOC and PT;
- Incidence of drug-related TEAEs by primary SOC and PT;
- Incidence of TEAEs by maximum severity, primary SOC and PT;
- Incidence of TEAEs by strongest relationship, maximum severity, primary SOC and PT;
- Incidence of TESAEs by primary SOC and PT;
- Incidence of TEAEs leading to study drug discontinuation by primary SOC and PT;
- Incidence of TEAEs leading to dose modification by primary SOC and PT.

In addition, the following primary parameter will be evaluated in **Part A** based on MTD analysis set population:

- MTD of Givinostat.

All outputs for safety outcomes will be based on the SAF analysis set, and presented by DLs (**Part A** only). There will be no planned statistical comparisons among treatment groups for safety data.

ADVERSE EVENTS

AE Investigator terms will be assigned to a PT and will be classified by primary SOC. AEs will be coded using the 20.1 version of MedDRA dictionary. TEAEs are defined as adverse events started at or after the first administration of study treatment.

See Appendix 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case (i.e. TEAE).

An overall summary of number of patients within each of the categories described in the sub-section below, will be provided as specified in the templates. Listings will include AEs and TEAEs.

A case narrative for each AE leading to treatment discontinuation (the "Action Taken with Study Drug" in section "AE" of the electronic CRF is "Definitively withdrawn"), and/or leading to death (see below), and/or ongoing at the end of treatment (the "Outcome" in the section "AE" of the electronic CRF is "Ongoing" at the time of database look) will be reported in the Clinical Study Report.

ALL TEAEs

Incidence of TEAEs will be presented by primary SOC and PT and also broken down further by maximum severity and relationship to Study medication.

SEVERITY AND COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

AEs will be graded by the Investigators according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, dated 14th June 2010. The grade assigned by the Investigator will be used for this analysis.

TEAEs starting after the first dose of Study medication (i.e. C1D1) with a missing severity will be classified as "severe*" (i.e. "grade 3*"), in order to distinguish them from the TEAEs graded as severe that will be reported without "*" (i.e. "severe").

If a patient reports a TEAE more than once within that SOC/PT, the AE with the worst severity will be used in the corresponding severity summaries.

RELATIONSHIP TO STUDY MEDICATION

In electronic CRF the relationship of an AE with the Study drug is classed as "Not Related", "Related" or "Unknown", based on Investigator's judgment.

A "Related" TEAE is defined as a TEAE with a relationship to the Study medication; in this case, the Investigator ticked "Related" in the field "Relationship with Study Drug" of the section "AE" of the electronic CRF.

A "Not Related" TEAE is defined as a TEAE without a reasonable relationship to the Study medication; in this case, the Investigator ticked "Not Related" in the field "Relationship with Study Drug" of the section "AE" of the electronic CRF.

If a TEAE is reported as "Unknown" in the field "Relationship with Study Drug" of the section "AE" of the electronic CRF even after the database lock, the worst relationship will be considered (i.e. "Related*). TEAEs with a missing relationship to Study medication even after the database look, the worst relationship will be considered (i.e. "Related*"). In both cases, the "*" will allow to distinguish them from the TEAEs considered by the Investigators as "Related" and reported without "*" (i.e. "Related").

If a patient reports the same TEAEs more than once within that SOC and/or PT, the TEAE with the worst case relationship to Study medication will be used in the corresponding relationship summaries.

TEAES LEADING TO DISCONTINUATION OF STUDY MEDICATION

TEAEs leading to permanent discontinuation of Study medication will be identified by using the

response on "Action taken with Study Drug" ticked as "Definitively withdrawn" from the section "AE" of the electronic CRF.

For TEAEs leading to discontinuation of Study drug, summaries of incidence rates (i.e. frequencies and percentages) by SOC and PT will be presented.

ADVERSE EVENTS LEADING TO DEATH

If any patients died during the Study, as recorded on the sections "EOS" and/or "AE" of the electronic CRF, the information will be presented in a summary table and a data listing.

TEAEs leading to death will be identified by using the following responses on the section "AE" of the electronic CRF:

- "Yes" at the question "Is this a serious event?" (death details);
- "Fatal" on the field "Outcome";
- "Death related to AE" on the field "Severity".

A summary of TEAEs leading to death by SOC and PT will be prepared.

All details of TEAEs leading to Death (date of death, autopsy performed and date of autopsy, if applicable, and death due to of Progression of the disease), recorded on "Death report" page on eCRF, will be listed only.

A case narrative for each death will be reported in the Clinical Study Report.

DOSE LIMITING TOXICITIES

A DLT is defined as one of the following drug-related toxicity:

- Grade 4 haematological toxicities, or
- Grade 3 febrile neutropenia, or
- Grade ≥ 3 non-haematological toxicities with exception of:
  a) Grade 3 diarrhoea without adequate supportive care lasting less than 3 days, and
  b) Grade 3 nausea or vomiting without adequate supportive care lasting less than 3 days, or
- Any drug-related SAE, or
- Any toxicity that is clearly not related to disease progression or intercurrent illness requiring interruption of dosing for more than 3 days during the first cycle.

The severity of the above mentioned events is graded by the Investigators according to CTCAE v. 4.03,

dated 14th June 2010.

Only DLTs experienced during the first cycle of treatment (i.e. up to C1D28) of **Part A** are considered for dose escalation decisions. DLTs include all AEs that are clearly not related to disease progression or intercurrent illnesses. Patients who didn't experience a DLT and missed more than 10% of the doses in Cycle 1 of **Part A** are replaced.

DLTs will be identified by using the response "Yes" at the question "Was this a Dose Limiting Toxicity Event?" on the section "AE" of the electronic CRF.

A summary of DLT by SOC and PT will be prepared.

A case narrative for each DLT will be reported in the Clinical Study Report.

SERIOUS ADVERSE EVENTS

SAEs will be identified by using the response on "Is this a serious event?" ticked as "Yes" on the "AE" section of the electronic CRF. A summary of SAE and Treatment Emergent SAEs (TESAEs) by SOC and PT will be prepared.

A case narrative for each SAE will be reported in the Clinical Study Report.

17.2. PART B

The following primary efficacy parameters will be evaluated in **Part B** **after 3 cycles of treatment** (i.e. at the end of Cycle 3) based on ITT analysis set and PP analysis set:

- **For PV and ET** (*if any*)**:** Complete response (CR) and partial response (PR) rate according to clinico-haematological ELN response criteria [1];
- **For MF** (*if any*)**:** CR, major response, moderate response and minor response rate according to the EUMNET response criteria [7].

Note that only in case the enrolment in **Part A** is slow (i.e. < 5 patients enrolled in 3 months, the eligibility for this part of the study could be expanded to all patients with cMPN.

The clinico-haematological ELN response criteria [1] and EUMNET response criteria will be used to assess the preliminary efficacy of Givinostat (primary endpoint) after 3 cycles of treatment in **Part B** for PV/ET and MF patients, respectively.

In all cases, the medical judgment of the Investigator's is taken into account. In particular, if the Investigator's clinical response assessment – that takes into account the overall medical judgment of the

specific patient's case - is not in agreement with the exact application of the clinico-haematological ELN or EUMNET response criteria , the Investigator's assessment will supersede the "mathematical" application of these criteria and used for analysis into study report. Also mathematical application of ELN response criteria (not agreed by the medical site team) will be analyzed.

Frequency and percentage of patients in each response category (CR, PR, no response (NR) for PV and ET; CR, major response, moderate response, minor response and NR rate for MF) will be presented at Cycle 3 Day 28 (C3D28). Of note, patients who dropped the study due to drug-related TEAE(s) before that the post-baseline efficacy measurement is obtained (i.e. at C3D28 and/or at C6D28), the post-baseline efficacy measurements (i.e. at C3D28 and/or at C6D28) will be considered as "No Response*", even if these assessments were not performed. "*" will allow to distinguish them from them from the therapeutic response evaluation result of "No Response", that will be reported without "*" (i.e. "No Response"). Other missing data will not be replaced, if not otherwise specified.

For **Part B** – Stage 1, Simon's design hypothesis will be evaluated by calculating the frequency and 95% CI of patients with a CR and/or PR at C3D28.

For Part B – Stage 2, the efficacy of Givinostat will be evaluated by means of a generalized linear model (logit link function and binomial distribution) adjusting for age, sex and disease type (PV, ET, MF). The therapeutic response will be collapsed in two categories in order to improve the model performance:

- For PV and ET:
  a) "Responders" (i.e. CR and PR), and
  b) "Not Responders" (i.e. NR);
- For MF:
  a) "Responders" (i.e. CR, major response, moderate response and minor response), and
  b) "Not Responders" (i.e. NR for MF).

In addition, the following primary safety parameters will be evaluated in **Part B** **after 3 cycles of treatment** (i.e. at the end of Cycles 3, or including data related to Cycles 1, 2 and 3) based on SAF analysis set:

- Number of patients experiencing AEs.
- Type, incidence, and severity of treatment-related AEs, graded according to CTCAE v. 4.03 (14th June 2010).

AEs will be coded using MedDRA dictionary (using the 20.1 version). AEs will be reported on a per patient basis. If a patient has more than one AE for a treatment that is coded to the same PT, the patient will be counted only once for that PT. Similarly, if a patient has more than one AE for a treatment within a SOC category, the patient will be counted only once in that SOC category. A patient with multiple CTCAE grades for an AE will be summarised under the maximum CTCAE grade recorded for the event.

Any AE which started at or after the first administration of Study treatment will be considered a TEAE. If the start date is missing for an AE, the AE will be considered to be treatment emergent.

An overview of AEs including the number of patients with at least one AE, at least one TEAE, at least one drug-related TEAE, at least one TESAE, any SAE, any AE leading to death, any TEAE leading to death, any TEAE leading to drug discontinuation, at least one grade ≥ 3 TEAE, will be presented. The following AE frequency tables will be also provided:

- Incidence of TEAEs by primary SOC and PT;
- Incidence of drug-related TEAEs by primary SOC and PT;
- Incidence of TEAEs by maximum severity, primary SOC and PT;
- Incidence of TEAEs by strongest relationship, maximum severity, primary SOC and PT;
- Incidence of TESAEs by primary SOC and PT;
- Incidence of TEAEs leading to study drug discontinuation by primary SOC and PT;
- Incidence of TEAEs leading to dose modification by primary SOC and PT.

The primary safety parameters will be evaluated in **Part B <u>after 3 cycles of treatment</u>** (i.e. at the end of Cycles 3, or including data related to Cycles 1, 2 and 3) based on SAF analysis set and taking into account the same rules describes in the paragraphs 17.1.

18. SECONDARY OUTCOMES

18.1. PART A

The following secondary efficacy parameters will be evaluated in **Part A <u>after 3 and 6 cycles of treatment</u>** (i.e. at the end of Cycles 3 and 6, respectively) based on ITT analysis set and PP analysis set:

- Preliminary efficacy of Givinostat (secondary endpoint) for PV/ET and MF patients, respectively:
  - **For PV and ET** (*if any*)**:** CR and PR rate according to the clinico-haematological ELN response criteria [1];
  - **For MF** (*if any*)**:** CR, major response, moderate response and minor response rate according to the EUMNET response criteria [7].

In all cases, the medical judgment of the Investigator's is taken into account. In particular, if the Investigator's clinical response assessment – that takes into account the overall medical judgment of the specific patient's case - is not in agreement with the exact application of the clinico-haematological ELN or EUMNET response criteria , the Investigator's assessment will supersede the "mathematical"

application of these criteria and used for analysis into study report. Also mathematical application of ELN response criteria (not agreed by the medical site team) will be analyzed.

Note that only in case the enrolment in **Part A** is slow (i.e. < 5 patients enrolled in 3 months, the eligibility for this part of the study can be expanded to all patients with cMPN.

Frequency and percentage of patients in each response category (CR, PR, NR rate for PV and ET; CR, major response, moderate response, minor response and NR rate for MF) will be presented at C3D28 and at Cycle 6 Day 28 (C6D28).

Of note, patients who dropped the study due to drug-related TEAE(s) before that the post-baseline efficacy measurement is obtained (i.e. at C3D28 and/or at C6D28), the post-baseline efficacy measurements (i.e. at C3D28 and/or at C6D28) will be considered as "No Response*", even if these assessments were not performed. "*" will allow to distinguish them from them from the therapeutic response evaluation result of "No Response", that will be reported without "*" (i.e. "No Response"). Other missing data will not be replaced, if not otherwise specified.

The following secondary parameter will be evaluated in **Part A** based on PK analysis set:

- Individual Givinostat concentrations tabulated by DL along with descriptive statistics.

Plasma concentrations from **Part A** will be listed and tabulated by dose and time point for all patients and time points with at least 1 PK assessment.

Descriptive statistics for all PK parameters for **Part A** will be calculated.

18.2. PART B

The following secondary efficacy parameter will be evaluated in **Part B after 6 cycles of treatment** (i.e. at C6D28) based on ITT analysis set and PP analysis set:

- Preliminary effectiveness of Givinostat (secondary endpoint) after 6 cycles of treatment in **Part B** for PV/ET and MF patients, respectively:
  - **For PV and ET** (*if any*)**:** CR and PR rate according to the clinico-haematological ELN response criteria [1];
  - **For MF (if any):** CR, major response, moderate response and minor response rate according to the EUMNET response criteria [7].

In all cases, the medical judgment of the Investigator's is taken into account. In particular, if the Investigator's clinical response assessment – that takes into account the overall medical judgment of the specific patient's case - is not in agreement with the exact application of the clinico-haematological ELN or EUMNET response criteria , the Investigator's assessment will supersede the "mathematical" application of these criteria and used for analysis into study report. Also mathematical application of ELN response criteria (not agreed by the medical site team) will be analyzed. Note that only in case the

enrolment in **Part A** is slow (i.e. < 5 patients enrolled in 3 months), the eligibility for this part of the study can be expanded to all patients with cMPN.

Frequency and percentage of patients in each response category (CR, PR and NR rate for PV and ET; CCR, major response, moderate response, minor response and NR rate for MF) will be presented at C6D28. Of note, patients who dropped the study due to drug-related TEAE(s) before that the post-baseline efficacy measurement is obtained (i.e. at C3D28 and/or at C6D28), the post-baseline efficacy measurements (i.e. at C3D28 and/or at C6D28) will be considered as "No Response*", even if these assessments were not performed. "*" will allow to distinguish them from them from the therapeutic response evaluation result of "No Response", that will be reported without "*" (i.e. "No Response"). Other missing data will not be replaced, if not otherwise specified.

The following secondary safety parameter will be evaluated in **Part B after 6 cycles of treatment** (i.e. at C6D28, or including data related to Cycle 4 Day 28 (C4D28), Cycle 5 Day 28 (C5D28) and any unscheduled visit included in that interval period) based on SAF analysis set:

- Number of patients experiencing AEs.
- Type, incidence, and severity of treatment-related AEs, graded according to CTCAE v. 4.03 (14th June 2010).

AEs will be coded using MedDRA dictionary (using the 20.1 version). AEs will be reported on a per patient basis. If a patient has more than one AE for a treatment that coded to the same PT, the patient will be counted only once for that PT. Similarly, if a patient has more than one AE for a treatment within a SOC category, the patient will be counted only once in that SOC category. A patient with multiple CTCAE grades for an AE will be summarised under the maximum CTCAE grade recorded for the event.

Any AE which started at or after the first administration of study treatment will be considered a TEAE. If the start date is missing for an AE, the AE will be considered to be a TEAE.

TEAE included in this analysis are defined as those starting after the date of the first administration of Cycle 4.

An overview of AEs including the number of patients with at least one AE, at least one TEAE, at least one drug-related TEAE, at least one TESAE, any SAE, any AE leading to death, any TEAE leading to death, any TEAE leading to drug discontinuation, at least one grade ≥ 3 TEAE, will be presented. The following AE frequency tables will be also provided:

- Incidence of TEAEs by primary SOC and PT;
- Incidence of drug-related TEAEs by primary SOC and PT;
- Incidence of TEAEs by maximum severity, primary SOC and PT;
- Incidence of TEAEs by strongest relationship, maximum severity, primary SOC and PT;
- Incidence of TESAEs by primary SOC and PT;
- Incidence of TEAEs leading to study drug discontinuation by primary SOC and PT;

- Incidence of TEAEs leading to dose modification by primary SOC and PT.

These secondary safety parameters will be evaluated in **Part B** **after 6 cycles of treatment** (i.e. at C6D28, or including data related to C4D28, C5D28 and any unscheduled visit included in that interval period) based on SAF analysis set and taking into account the same rules describes in the paragraphs 17.1.

The following secondary parameters will be evaluated in **Part B** based on PK analysis set:

- Individual Givinostat concentrations tabulated with descriptive statistics: plasma concentrations from **Part B** will be listed and tabulated by time point for all patients and time points with at least 1 PK assessment; descriptive statistics for all PK parameters for **Part B** will also be calculated; these tables will include number of observations, mean, standard deviation, median, minimum and maximum and additionally the geometric mean and Coefficient of Variation (CV), not for time to maximum plasma concentration.

18.3. PK ANALYSIS

PK analyses will be carried-out by Accelera using Phoenix WinNonlin 6.3 (Certara Company).

For both **Part A and B**, PK parameters of Givinostat and its metabolites (ITF-2374 and ITF-2375) will be: Cmax, Clast, CTmax, AUClast and if data permit and only for Givinostat AUC(0- τ), Ro (observed accumulation ratio on Cmax, AUClast and if data permit AUC(0-τ)) and Ratio ITF-2374 parent or ITF-2375/parent Cmax and AUClast.

The actual plasma sampling times will be used in the analysis.

For the PK calculation, plasma concentrations below the lower limit of quantification (BLQ) will be treated as follows:

- All BLQ values before the first detectable concentration will be set equal to zero.
- All BLQ values after the last detectable plasma concentration will be excluded .
- BLQ value between two detectable plasma concentrations will be excluded.

For the descriptive statistic calculation on plasma concentration data, the BLQ values will be treated as follows:

- BLQ values will be set equal to zero.
- BLQ values between two detectable plasma concentrations will be excluded.

Individual values considered to be anomalous will be excluded from the pharmacokinetic analysis and descriptive statistics. Justification for exclusion will be provided in the pharmacokinetic report.

The following PK plasma parameters will be calculated for **both part A and B**:

- Tmax,
- Tlast,
- Cmax,
- Clast,
- Cτ,
- AUClast

and if data permit AUC(0- τ) and Ro (observed accumulation ratio on Cmax and AUClast and if data permit AUC(0- τ)) between the individual parameter obtained on Day 28 to the corresponding one on Day 1.

Pharmacokinetic parameters will be calculated as follows:

- Tmax,
- Tlast,
- Cmax,
- Clast

and Cτ will be taken directly from the raw data.

Areas under the plasma concentration vs. time curve (AUClast, AUC(0-τ)) will be calculated using linear trapezoidal rule.

Accumulation ratios Ro on Cmax, AUClast and if data permit on AUC(0- τ) will be calculated as the ratio between the individual parameter obtained on Day 28 to the corresponding one on Day 1. Ratios between metabolites (ITF-2374 and ITF-2375) to parent drug will be performed on Cmax and AUClast on day 1 and day 28.

Descriptive statistics of plasma concentrations and pharmacokinetic parameters of Givinostat will include N, Mean, SD, Coefficient of Variation (CV) Median, Minimum, and Maximum.

The following units will be used for individual and mean parameters of the compound:

- Cmax, Clast, C τ: ng/mL,
- Tmax, Tlast: hr,
- AUCs: ng·hr/mL.

Descriptive statistics of plasma concentrations and pharmacokinetic parameters of Givinostat will include N, Arithmetic Mean, SD, Geometric Mean, Coefficient of Variation (%), Min, Median and Max.

Appropriate statistical methods will be applied to analyze accumulation ratio (R0) and dose proportionality.

In particular, to estimate the extent of accumulation after repeat dosing, the observed accumulation ratio will be determined using Cmax and AUClast and if data permit AUC(0- τ) log-transformed values.

A mixed effect model will be implemented with day as fixed effect and patient as a random effect. Day 28 will be compared vs Day 1 for each dose level. Again, the 90% CIs for the differences will be calculated and back-transformed.

Due to the scheme in dose escalation and the study design (parallel groups), the dose proportionality evaluation will be approached with a pure explorative intent. AUClast, Cmax and if the data permit AUC(0- τ) following repeat doses will be used for a preliminary assessment being aware the results should be interpreted with caution. The method foresees to apply the power model approach where the slope of the line obtained by regressing log(PK parameter) on log(dose) will be estimated and presented together with its 90% CI. Dose-proportionality implies a CI of regression coefficient (b as below) including 1 in the following model:

$$\log(\text{PK parameter}) = a + (b \cdot \log(\text{dose})) + \varepsilon$$

where a is the intercept, b the slope and ε the random error term.

19. EXPLORATORY OUTCOMES

19.1. PARTS A AND B

The following exploratory parameters will be evaluated using ad-hoc descriptive analysis in **Parts A** and **B** based on ITT analysis set and PP analysis set:

- The effect of Givinostat on each single response parameter according to the clinico-haematological ELN (for PV and ET) [1] and EUMNET response criteria (for MF) [7]; note that only in case the enrolment in Part A is slow (i.e. < 5 patients enrolled in 3 months), the eligibility for this part of the study could be expanded to all patients with cMPN.
- Effects of Givinostat on PD markers.
- Effects of Givinostat on spleen size in patients with confirmed splenomegaly at baseline.
- Improvement of constitutional symptoms evaluated according to MPN-SAF QOL questionnaire [8, 9] including patients without the symptom of headache, pruritus and microvascular symptoms (i.e MPN SAF Score =0) and number and percentage of patient with symptom score from 0 to 3; from 4 to 6 and more than 7.

- Reduction of the JAK2V617F allele burden, tested by quantitative RT-PCR.
- Reduction of the symptomatic treatment of pruritus in term of dosage and/or days of treatment.

The following exploratory parameters will be evaluated using ad-hoc descriptive analysis in Part B based on ITT analysis set and PP analysis set:

- The preliminary efficacy of Givinostat after 6 cycles of treatment according to the "new" ELN criteria (i.e. revised ELN response criteria) [2]. In all cases, the medical judgment of the Investigator's is taken into account. In particular, if the Investigator's clinical response assessment – that takes into account the overall medical judgment of the specific patient's case - is not in agreement with the exact application of the revised clinico-haematological ELN response criteria , the Investigator's assessment will supersede the "mathematical" application of these criteria and used for analysis into study report. Also mathematical application of ELN response criteria (not agreed by the medical site team) will be analyzed.
- The effect of Givinostat on single parameters of the "new" ELN response criteria (i.e. revised ELN response criteria) [2].

The "**new**" ELN response criteria [2] are detailed in the paragraph 4.8.7 of the Study protocol.

Explorative endpoints will be summarised by descriptive methods based on ITT analysis set and PP analysis set. Default summary statistics and changes from baseline (*where applicable*) to each time point for all parameters will be produced.

20. OTHER SAFETY OUTCOMES

All patients who receive at least one dose will be included in the safety evaluation.

Safety data including laboratory evaluations, physical exams, ECG monitoring and vital signs assessments will be summarised at each time point.

Descriptive statistics (arithmetic mean, standard deviation, median, minimum and maximum) will be calculated for quantitative safety data as well as for the difference from baseline, *if applicable*. Frequency counts will be compiled for classification of qualitative safety data.

In addition, a shift table describing out of normal range shifts (low/normal/high values) will be provided for clinical laboratory results.

A normal-abnormal shift table will also be presented for physical exam and ECG results.

20.1. LABORATORY EVALUATIONS.

Results from the local laboratories will be included in the reporting of this study for Haematology,

Blood Chemistry and Urinalysis.

A list of laboratory assessments to be included in the outputs is included in the paragraph 4.7.1 of the Study protocol.

Outputs will be based on the SAF analysis set, presented by DL (for **Part A only**), and will use the International System (SI) Units.

The following summaries will be provided for Haematology, Blood Chemistry, Urinalysis laboratory data by DL (for **Part A only**):

- Actual and change from baseline by visit (for quantitative measurements);
- Shift from baseline according to normal range criteria (for categorical measurements);
- Presence/absence, with number (n) and percentage (%), where applicable (i.e. Glucose and Protein, for Urinalysis test).
- Listing of laboratory data by Study Part and patient ID;
- Listing of patients with clinically significant abnormal values, as reported in electronic CRF based on Investigator's judgment;
- Listing of patients with markedly significant abnormal values (e.g. grade 3 thrombocytopenia as per CTCAE version 4.03).

20.2. LABORATORY SPECIFIC DEVIATIONS

To convert from each local laboratory conventional unit to the SI unit, values will be multiplied by the conversion factor:

Component	Conventional Unit	Conversion Factor	SI Unit
Haematology			
Haematocrit	%	0.01	Proportion of 1.0
Haemoglobin	g/dL	10	g/L
RB count	x 10^6/µL	1	x 10^{12}/L

Platelets	x 10^3/µL	1	x 10^9/L
WB count	x 10^3/µL	1	x 10^9/L
Basophils	x 10^3/µL	1	x 10^9/L
Eosinophils	x 10^3/µL	1	x 10^9/L
Lymphocytes	x 10^3/µL	1	x 10^9/L
Monocytes	x 10^3/µL	1	x 10^9/L
Neutrophils	x 10^3/µL	1	x 10^9/L
Mean Corpuscular Volume	fL	1	µm^3
Mean Corpuscular Haemoglobin	Pg	0.062	fmol
Mean Corpuscular Haemoglobin Concentration	g/dL	10	g/L
Blood Chemistry			
Sodium	mEq/L	1.0	mmol/L
Potassium	mEq/L	1.0	mmol/L
Calcium	mg/dL mEq/L	0.25 0.50	mmol/L
Chloride	mEq/L	1	mmol/L
Magnesium	mg/dL	0.4114	mmol/L
Albumin	g/dL	10	g/L
Blood Glucose	mg/dL	0.0555	mmol/L
BUN	mg/dL	0.357	mmol/L
Urea	mg/dL	0.357	mmol/L

Creatinine	mg/dL	88.4	µmol/L
Alanine aminotransferase (ALT)	U/L	1	U/L
Aspartate aminotransferase (AST)	U/L	1	U/L
Alkaline phosphatase	U/L	1	U/L
Total Bilirubin	mg/dL	17.104	µmol/L
Lactate Dehydrogenase	U/L	1	U/L
Urinalysis			
pH	(unitless)		
Specific Gravity	(unitless)		
Glucose	mg/dL	0.0555	mmol/L
Protein	g/dL	10.0	g/L

LABORATORY REFERENCE RANGES AND MARKEDLY ABNORMAL CRITERIA

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in local units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

Potentially clinically significant laboratory values will be summarised by laboratory variable. Platelets values will be evaluated as a potentially clinically significant low value at any time during the study, and will be presented by visit.

The Platelets potentially clinically significant low value is defined as follows:

- Platelets count < 150 x 10^9/L but > 75 x 10^9/L (i.e. grade 1 thrombocytopenia as per CTCAE version 4.03);
- Platelets count < 75 x 10^9/L but > 50 x 10^9/L (i.e. grade 2 thrombocytopenia as per CTCAE version 4.03);
- Platelets count < 50 x 10^9/L but > 20 x 10^9/L (i.e. grade 3 thrombocytopenia as per CTCAE version 4.03);
- Platelets count < 25 x 10^9/L (i.e. grade 4 thrombocytopenia as per CTCAE version 4.03).

20.3. ECG EVALUATIONS

Results from the ECG will be based on the SAF analysis set, presented by DL (for **Part A only**)

The following ECG variables will be reported for this study:

Qualitative Evaluations:

- Overall assessment of ECG (Investigator's judgment Interpretation):
  - Normal
  - Abnormal - Not Clinically Significant;
  - Abnormal - Clinically Significant.

All the abnormalities – including the details of detected "Findings" as reported on electronic CRF - will be listed.

  - RR Interval (msec);
  - QT Interval (msec);
  - QTc Interval (msec) – automatically calculated on electronic CRF using the Bazett's correction formula.

The following summaries will be provided for ECG data:

  - The number (n) and percentage (%) from baseline by visit for qualitative interpretation;
  - Actual and change from baseline by visit for quantitative measurements;

- Shift from baseline according to markedly abnormal criteria for quantitative measurements;
- Listing of patients meeting markedly abnormal criteria for quantitative measurements;

ECG SPECIFIC DERIVATIONS

Bazett's Correction (msec) is derived directly from eCRF and it is calculated as follows:

- $QTc\ (\text{msec}) = \frac{QT\ (msec)}{\sqrt{RR(sec)}}$

Where, RR Interval, imputed directly on the eCRF by the investigator, is calculated as follows:

- $RR\ (\text{sec}) = \frac{60}{HR\ (bpm)}$

ECG MARKEDLY ABNORMAL CRITERIA

Markedly abnormal quantitative ECG measurements will be identified in accordance with the following predefined markedly abnormal criteria:

- Absolute values for QTc interval > 450 msec
- Change from Baseline for QTc interval >30 msec increase from baseline

20.4. SPLEEN EVALUATIONS

Results from the Spleen evaluation will be based on the SAF analysis set and presented by Cohort (Part A only).

The following spleen variables will be reported for this study:

- Imaging Technique of Spleen:
  - MRI;
  - CT Scan.
- Qualitative Evaluation: Overall assessment of Spleen (Investigator's judgment Interpretation):
  - Normal;
  - Abnormal, Not Clinically Significant;

- Abnormal, Clinically Significant.

The Abnormalities will be listed.

- Quantitative Evaluations:
  - Longitudinal Diameter (cm);
  - Antero/Posterior Diameter (cm);
  - Transversal Diameter (cm);
  - Splenic Volumetric Index (cm^3) - automatically field on eCRF.

The following summaries will be provided for Spleen data:

- The number (n) and percentage (%) at baseline for Technique of Imaging;
- The number (n) and percentage (%) at baseline for qualitative interpretation;
- The number (n) and percentage (%) at baseline, Cycle 3 Day 28 and Cycle 6 Day 28 showed a Spleen Volume reduction ≥ 35%.

Spleen Specific Derivations: Splenic Volumetric Index (cm^3) is automatically calculated by electronic CRF as following:

$$SVI\ (cm^3) = \frac{(Longitudinal * \text{Antero/Posterior} * \text{Transversal})\ \text{Diameters}}{27}$$

20.5. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Systolic Blood Pressure (mmHg);
- Diastolic Blood Pressure (mmHg);
- Heart Rate (bpm);
- Respiratory Rate (breaths/min);
- Body Temperature (°C);
- Height (cm), only for Baseline;
- Weight (kg);

The following summaries will be provided for vital signs data:

- Actual and change from baseline by visit;
- Listings of all measurements by DL (for **Part A only**) and patient ID.

20.6. PHYSICAL EXAMINATION

The following summaries will be provided for physical examination data:

- Incidence of abnormalities at screening;
- Incidence of abnormalities post baseline.

20.7. OTHER SAFETY ASSESSMENTS

No other safety assessment will be collected for this study.

21. MOLECULAR ANALYSIS

Results from the molecular analysis performed during the Study will be listed, including results from pharmacodynamic (PD) markers.

The following information will be provided for $JAK2^{V617F}$ allele burden evaluations:

- $JAK2^{V617F}$ positivity (Yes/No);
  - Qualitative evaluation of JAK2V617F allele burden
    - Heterozygous
    - Homozygous
- Quantitative evaluation of JAK2V617F allele burden (%);
- Actual and change from baseline by visit;
- Number (n) and percentage (%) of patients with:
  - a reduction of any specific molecular abnormality to undetectable levels;

  - a reduction of ≥ 50% from baseline value in patients with < 50% mutant allele burden at baseline;
  - a reduction of ≥ 25% from baseline value in patients with > 50% mutant allele burden at baseline.
- Descriptive statistics of quantitative evaluation of $JAK2^{V617F}$ allele burden.

Notably, approximately 4.0 mL of blood for PD markers is collected before the first Givinostat dose (pre-dose) and 12 hours after the first Givinostat dose (post-dose) at C1D1 both in **Part A** and in **Part B** for measurement of levels of molecular markers, to evaluate the PD effect of Givinostat and to identify markers predictive of clinical benefit of Givinostat (see Appendix A of the Study protocol). In addition, PD evaluations are performed also using an aliquot of the PK samples collected at time points described in the paragraph 4.5.3.2 of the Study protocol. The molecular markers to be measured may include mRNA levels of JAK2, STAT5A, BclXL, PIM1, NFE2, LMO2, cMyc as well as HDAC3, STAT4, MYBL1, MEGF9, GLRX, FAM49A. The final list of PD markers to be measured will depend on ongoing scientific developments as well as availability of assays and other business considerations. For all time points an additional PD blood sample is collected as back-up sample.

This assessment is mandatory and is performed by a central laboratory. The exact date and time of the PD blood draws is recorded along with the date and time of the last dose of study drug preceding the blood draw.

All molecular examinations (e.g. $JAK2^{V617F}$ allele burden evaluated by quantitative RT-PCR, mRNA isolation, gene expression) are performed in a central laboratory.

The results are transcribed into the electronic CRF by the central laboratory team or its designee and the original signed and dated laboratory print-out/tracings are monitored and stored at the central laboratory.

After evaluation of preliminary results and data exploration, some additional analyses may be performed to identify and quantify other molecular parameters of interest in term of improving of the knowledge of cMPN and the activity of the drug in these disorders.

$JAK2^{V617F}$ allele burden (%) and changes (reductions) from baseline will be summarised using descriptive statistics (n, mean, SD, arithmetic CV (%), median, minimum and maximum) by dose level and time point.

A patient listing of all the relevant molecular examinations data ($JAK2^{V617F}$ allele burden, mRNA isolation, gene expression) will be presented by DL (for **Part A only**) and time point.

22. BONE MARROW ANALYSIS

A bone marrow histological evaluation is performed to all patients recruited that provided the specific consent in **Part B** in order to assess the presence of age adjusted normocellularity and/or trilinear hyperplasia as requested by the "new" ELN response criteria (i.e. the revised ELN response criteria) [2].

This examination is performed in the local laboratory of each site. The results of this test are transcribed into the electronic CRF and the original signed and dated laboratory print-out/tracings, including the assessment of the presence of age adjusted normocellularity and/or trilinear hyperplasia, is monitored and stored at the study site.

Notably, in case the patient performs the bone marrow histological evaluation as requested by the "new" ELN criteria (i.e. the revised ELN response criteria) [2] – i.e. bone marrow evolution including the assessment of the presence of age adjusted normocellularity and/or trilinear hyperplasia - 1 month before the study start (i.e. the signature of the "primary" ICF), this examination has not to be repeated for this Study in order to limit the discomfort for the patient. In any case, the results of this test are transcribed into the electronic CRF and the original signed and dated laboratory print-out/tracings, including the assessment of the presence of age adjusted normocellularity and/or trilinear hyperplasia, is monitored and stored at the study site.

In case the patient drops-out the Study during the first 3 Cycles (i.e. before the C3D28), this evaluation has not to be performed at EOS visit.

Finally, in case the patient refused to provide this written consent to perform the bone marrow evaluation, this patient can still be recruited in Part B. However, this patient will not be counted to assess the related exploratory endpoints (i.e. overall response rate of Givinostat at the MTD after 6 cycles according to the revised ELN response criteria [2], and the evaluation of the effect of Givinostat on each single response parameter according to the revised ELN response criteria [2]).

The following information will be provided for the bone marrow histological evaluation:

- Number (n) and percentage (%) of patient with marrow histological evaluation;
- Number (n) and percentage (%) of presence of age-adjusted normocellularity;
- Number (n) and percentage (%) of trilinear hyperplasia absence;
- Number (n) and percentage (%) of grade >1 reticulin fibrosis absence;
- Listing of reason of not performed evaluation.

23. DOSE MODIFICATION ANALYSIS

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patients to continue the treatment with the study drug.

The objective of the Givinostat dose adjustment rules is to optimize the response for each individual patient, avoiding specific drug-related toxicities. Therefore, dose reductions or interruptions will be mandatory for specific toxicities and dose increases after an initial dose reduction will be allowed in the case of inadequate efficacy at the reduced dosage in absence of specific toxicities.

In the Cycle 1 of **Part A** dose modifications will not be allowed. Patients receiving subsequent cycles of treatment in **Part A** may have up to two dose modifications for drug related DLT's.

Each dose modification has to be recorded on the CRF and the severity of the above mentioned events will be graded according to NCI Common Terminology Criteria for AE (CTCAE v. 4.03, 14th June 2010).

Reason for treatment discontinuation and number of patients treated beyond protocol-specified discontinuation criteria will also be summarised for the safety population.

The following information will be provided for the Dosage Change, by DL (**for Part A only**) and time point:

- Number (n) and percentage (%) of patient with dose temporarily stopped; dose restarted at previous dose; dose restarted and actual dose reduced; dose reduced; dose restarted and actual dose increased;
- Listing of start/end date, type of dose change, single dose (mg) and reason for Change/Interruption.

The calculation of the compliance, in percentage and collapsed in class (Too low, Adequate, Too high), as per Section 15.1 will be capture, for each patient, the deviation from the dose administration plan.

24. OVER-DOSAGE AND OTHER SITUATIONS PUTTING THE PATIENT AT RISK OF ADVERSE REACTION

In general, a drug overdose in a clinical trial is defined as the accidental or intentional use of a drug or medicine in an amount exceeding the protocol defined dose(s). In this Study, if an AE is associated with

("results from") the overdose of Givinostat, the AE is reported as an SAE, even if no other criteria for seriousness is met.

If a dose of Givinostat meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect." Any instance of overdose (suspected or confirmed, with and without an AE) has to be reported to the Sponsor within 24 hours and, only in case of AEs, it has to be fully documented as a SAE. Details of any signs or symptoms and their management should be recorded in the SAE Form including details of any antidote(s) or systematic treatment administered. Any signs or symptoms of over-dosage are treated symptomatically.

Any other situations putting the patient at risk of adverse reaction, such as misuse and abuse, medication errors, suspect of transmission of infective agents must be reported to the Sponsor within 24 hours and must be fully documented as a SAE.

Listing of patients with overdose reported as a non-serious Even will be provided.

25. PREGNANCY

Female patients who have a positive pregnancy test during the pre-treatment evaluations assessment are not eligible for Study participation. If a patient becomes pregnant while on Study, the treatment is immediately stopped.

Patients are instructed to notify the Investigator if, after completion of the study, it is determined that they became pregnant during the treatment phase or through 3 months after the last dose of study drug.

Whenever possible, a pregnancy with an onset within the above defined time frame is followed until termination, any premature termination is reported, and the status of the mother and child is reported as well after delivery.

If the Investigator is made aware that the partner of a male patient who is participating in the Study become pregnant, he/she is required to report the pregnancy.

Whenever possible, such pregnancy is followed until termination, any premature termination is reported, and the status of the mother and child is reported as well after delivery.

Listing of pregnant patients will be provided.

26. DATA NOT SUMMARISED OR PRESENTED

These variables and/or domains will not be summarised, but they will be listed:

- Comments, with the expection for ECI (if any);
- Investigator signature page*;
- Participation Status* (i.e. Is the patient continuing to the next visit?).

*These variables will not be listed, but will be available in the clinical study database.

27. REFERENCES

ICH E9 Statistical Principles of Clinical Trials (CPMP/ICH/363/96)

Study protocol (Study N.: DSC/12/2357/45; EudraCT N.: 2013-000860-27), version 1.0, dated 01st March 2013 and amendments (Amendment 1, dated 23rd July 2013, and Amendment 2, dated 29th July 2015).

1. Barosi G, Birgegard G, Finazzi G, Griesshammer M, Harrison C, Hasselbalch HC, Kiladjian JJ, Lengfelder E, McMullin MF, Passamonti F, Reilly JT, Vannucchi AM, Barbui T, *Response criteria for essential thrombocythemia and polycythemia vera: result of a European LeukemiaNet consensus conferenc*e, Blood. 2009 May 14; 113(20): 4829-33.
2. Barosi G., Mesa R., Finazzi G. et al., *Revised response criteria for polycythemia vera and essential thrombocythemia: a ELN and IWG-MRT consensus project*, Blood, 2013 June 6; 121(23): 4778-81.
3. Le Tourneau C, Lee JJ, Siu LL, *Dose Escalation Methods in Phase I Cancer Clinical Trials*, JNCI, 2009 May 20; 101(10): 708–720.
4. Rubinstein LV and Simon RM*, Phase I clinical trial design*, In Budman, Calvert, Rowinsky, (eds.), Handbook of Anticancer Drug Development, Elsevier, Amsterdam, 297-308, 2003.
5. Omura GA, *Modified Fibonacci Search*, J. Clin. Oncol., 2003 August 15; 21(16): 3177 – 3177.
6. Simon R., *Optimal two-stage designs for phase II clinical trials*, Controlled Clinical Trials, 1989; 10: 1-10.
7. Barosi G, Bordessoule D, Briere J et al., *Response criteria for myelofibrosis with myeloid metaplasia: results of an initiative of the European Myelofibrosis Network (EUMNET)*, Blood 2005; 106: 2849-53.
8. Scherber et al., *The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF): International Prospective Validation and Reliability Trial in 402 patients*, Blood, 2011 July 14; 118(2): 401-408.
9. Emanuel R.M., Dueck A.C., Geyer H.L. et al.: *Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs*, JCO November 20, 2012; 30 (33): 4098-4103.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

DATES & TIMES

Depending on data available, dates and times will take the form respectively

- yyyy-mm-dd or dd-mmm-yyy;
- hh:mm:ss.

SPELLING FORMAT

English UK.

PRESENTATION OF TREATMENT DOSE LEVELS

For MTD analysis set, DLs will be represented as follows and in that order:

Givinostat daily dose	Givinostat dose level (DL)	DL used primarily to asses	Label for Tables, Listings and Figures (TLFs)
100 mg b.i.d.	DL1 (first three patients)	MTD, PK, PD	DL1
	DL1 (additional three patients)		DL1 expanded
2 capsules of 50 mg at the morning AND 1 capsule of 50 mg at the evening (1.e. 12 hours after)	DL6	MTD, PK, PD	DL6
50 mg b.i.d.	DL0	Safety, PK, PD*	DL0

FOR PRESENTATION OF VISITS

For outputs, visits will be represented, if applicable, as follows and in that order:

Study Part	Visit	Visit label for Tables, Listings and Figures (TLFs)[1]
Part A	Screening Visit	A - Baseline
	Cycle 1 Day 1 Visit – PRE-DOSE	A - C1D1 – PRE
	Cycle 1 Day 1 Visit – POST-DOSE	A - C1D1 - POST
	Cycle 1 Day 2 Visit	A - C1D2
	Cycle 1 Day 3 Visit	A - C1D3
	Cycle 1 Day 4 Visit	A - C1D4
	Cycle 1 Day 8 Visit	A - C1D8
	Cycle 1 Day 10 Visit	A - C1D10
	Cycle 1 Day 15 Visit	A - C1D15
	Cycle 1 Day 22 Visit	A - C1D22
	Cycle 1 Day 28 Visit	A - C1D28
	Cycle 2 Day 28 Visit	A - C2D28
	Cycle 3 Day 28 Visit	A - C3D28
	Cycle 4 Day 28 Visit	A - C4D28
	Cycle 5 Day 28 Visit	A - C5D28
	Cycle 6 Day 28 Visit	A - C6D28
	End of Study Visit for completers patients	A – EOS
	Unscheduled Visit n. 1 – PRE-DOSE	A - UNSCHEDULED 1 – PRE*
	Unscheduled Visit n. 2 – PRE-DOSE	A - UNSCHEDULED 1 – PRE*
	…	…
	Unscheduled Visit n. *N* – PRE-DOSE	A - UNSCHEDULED *N* – PRE*
	Unscheduled Visit n. 1 – POST- DOSE	A - UNSCHEDULED 1 – POST*
	Unscheduled Visit n. 2 – POST- DOSE	A - UNSCHEDULED 2 – POST*
	…	…
	Unscheduled Visit n. *N* – POST-DOSE	A - UNSCHEDULED *N* – POST*
Part B	Screening Visit	B - Baseline
	Cycle 1 Day 1 Visit – PRE-DOSE	B - C1D1 – PRE

	Cycle 1 Day 1 Visit – POST-DOSE	B - C1D1 – POST
	Cycle 1 Day 28 Visit	B - C1D28
	Cycle 2 Day 28 Visit	B - C2D28
	Cycle 3 Day 28 Visit	B - C3D28
	Cycle 4 Day 28 Visit	B - C4D28
	Cycle 5 Day 28 Visit	B - C5D28
	Cycle 6 Day 28 Visit	B - C6D28
	End of Study Visit	B - EOS
	Unscheduled Visit n. 1 – PRE-DOSE	B - UNSCHEDULED 1 – PRE*
	Unscheduled Visit n. 2 – PRE-DOSE	B - UNSCHEDULED 1 – PRE*
	…	…
	Unscheduled Visit n. *N* – PRE-DOSE	B - UNSCHEDULED *N* – PRE*
	Unscheduled Visit n. 1 – POST- DOSE	B - UNSCHEDULED 1 – POST*
	Unscheduled Visit n. 2 – POST- DOSE	B - UNSCHEDULED 2 – POST*
	…	…
	Unscheduled Visit n. *N* – POST-DOSE	B - UNSCHEDULED *N* – POST*

1 In all cases, the day of the visit should be reported.* To be ordered on the basis of the date of the visit.

*Drop-out visit refers to patients who prematurely discontinued the treatment showing data recorded during their last assessment visit.

SCREENING FAILURES

Patients who sign an ICF but who do not start Study treatment for any reason, will be considered as "Screening Failures".

For screening failure patients, a separate Table will be produced including the primary reason for screen failure and patient's demographic information as per electronic CRF.

LISTINGS

All listings will be ordered by the following:

- Part A
  - DL group;
  - Patient ID;
  - Date (where applicable).
- Part B

Patient ID;

- Date (where applicable).

TEXT CASE

- For titles and column labels, capitalize important words, i.e. nouns, pronouns, verbs, adverbs and adjectives but not articles, conjunctions or prepositions.
- All Footnotes will be in sentence case format.
- All symbols used in body of outputs will be footnoted.
- Continuous Variables:
  - Number ("n"),
  - Mean,
  - Standard Deviation ("SD"),
  - Median,
  - Minimum ("min"),
  - Maximum ("max")

will be presented for all variables on the original scale.

- Categorical Variables:
  - Number ("n"),
  - Percentage (%)

in each category will be the default summary presentation.

- The percentage of patients in each category relative to the total number of patients in the relevant analysis population will be the default. Percentages relative to the total number of patients in the relevant analysis population with a non-missing assessment will be specified in a programming note on the shell if required.
- Where percentages are presented, a footnote will be added to explain what the denominator of the percentage is, in the form "Percentages are calculated relative to the total number of patients in the SAF" as the first footnote.
- All computed percentages will be presented using one decimal place except for where the percentage is 100 where no decimal places are presented.
- The percentage will be also presented if the count is zero.

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE

START DATE	STOP DATE	ACTION
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR/CONCOMITANT MEDICATIONS AND PRIOR/CONCOMITANT NON-DRUG THERAPIES:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

Statistical Analysis Plan Signature Page

Statistical Analysis Plan V2.2 (addendum) (Dated 21th March 2018) for a two-part study to assess the safety and preliminary efficacy of Givinostat in patients with JAK2^{V617F} positive Polycythemia Vera (Study N. DSC/12/2357/45; study protocol version 3.0, dated 29th July 2015).

	Name	Signature	Date
Author:	PPD	PPD	22 March 2018
Position:	Biostatistician 2		
Company:	Quintiles		

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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Company: Italfarmaco S.p.A.			

OUTPUT TEMPLATES SIGNATURE PAGE

Output Templates V2.2 (Addendum) (Dated 21th March 2018):

- **Part A:** Analyses to determine the Maximum Tolerated Dose (MTD);
- **Part B (I):** Stage I (Interim Analysis) of the Simon's 2-stage design (Primary evaluation of Response Rate)
- **Part B (II):** Stage 2 (Overall Analysis) of the Simon's 2-stage design (at the end of Part B).

For a two-part study to assess the safety and preliminary efficacy of Givinostat in patients with JAK2^{V617F} positive Polycythemia Vera (Study N.: DSC/12/2357/45; study protocol version 3.0, dated 29th July 2015).

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Upon review of this document, the undersigned approves this version of the Output Templates, authorizing that the content is acceptable for the reporting of this study.

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