STUDY N.: DSC/12/2357/45
EUDRACT N.: 2013-000860-27

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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EMERGENCY SAFETY PROCEDURES

Any SAE (see chapter "Adverse Events" for definition and details), that occurs after a patient has signed the Informed Consent Form and up to the follow-up visit (regardless of relationship to study drug) must be reported by the Investigators to Italfarmaco S.p.A. within **24 hours** of learning of its occurrence.

Related SAEs MUST be collected and reported even if the study has been closed.

The Investigator must notify the SAE to the Drug Safety Unit (hereinafter "DSU") of Italfarmaco S.p.A. by sending the SAE Form, according with the procedures described in the study manual and within 24 hours of learning of its occurrence.

The details of the DSU are specified below:

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SIGNATURE PAGES

Compound name: **Givinostat**
Study number: **DSC/12/2357/45**
EudraCT number: **2013-000860-27**

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CENTRE SIGNATURE

Compound name: **Givinostat**
Study number: **DSC/12/2357/45**
EudraCT number: **2013-000860-27**

I have read and understood this clinical study protocol (version 3.0, 29th July 2015) that includes the Amendment 2 (version 1.0, 29th July 2015), and agree to conduct this trial in accordance with all stipulations of the clinical study protocol (version 3.0, 29th July 2015) that includes the Amendment 2 (version 1.0, 29th July 2015), and in accordance with the Good Clinical Practice.

Principal Investigator's Name	*Signature*	*Date*

Centre address

Phone number

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GLOSSARY OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutical Classification
BED	Biologically Effective Dose
b.i.d.	Bis In Die (twice daily)
BUN	Blood Urea Nitrogen
Ca	Calcium
CHMP	Committee for Medicinal Products for Human Use
CIs	Confidence Intervals
Cl	Chloride
cMPN	Chronic Myelo-Proliferative Neoplasms
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CMO	Contact Manufacturing Organization
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for AE
DSU	Drug Safety Unit
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELN	European LeukemiaNet
EMA	European Medicinal Agency
ET	Essential Thrombocytopenia
EU	European Union
EUMNET	European Myelofibrosis Network
GCP	Good Clinical Practice
Hb	Haemoglobin
HBV	Hepatitis B Virus
HCT	Haematocrit
HCV	Hepatitis C Virus

HDACs	Histone deacetylases
HDPE	High-density Polyethylene
HGF	Haematopoietic Growth Factor
HIV	Human Immunodeficiency Virus
IC50	50% Inhibitory Concentration
ICH	International Conference on Harmonization
IF	Investigator's File
IMP	Investigational Medicinal Product
IRB/EC	Institutional Review Board/Ethics Committees
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
LDPP	Low Denier Polypropylene
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
o.d.	Once Daily
PB	Peripheral Blood
PD	Pharmacodynamic
PLT	Platelets

PMF	Primary Myelofibrosis
PP	Per-protocol
PR	Partial Response
PRV-1	Polycythemia Rubra Vera Receptor 1
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
SOP	Standard Operative Procedure
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)
TMF	Trial Master File
ULN	Upper Limit of Normal
WBC	White Blood Cell (count)
WHO	World Health Organization
WHO-DRL	World Health Organization-Drug Reference List

STUDY SYNOPSIS

STUDY TITLE	A two-part study to assess the safety and preliminary efficacy of Givinostat in patients with $JAK2^{V617F}$ positive Polycythemia Vera.
STUDY NUMBER	DSC/12/2357/45
EUDRACT No.	2013-000860-27
STUDY TYPE	International
CLINICAL PHASE	Ib/II
DISEASE	Patients with JAK2 positive chronic myeloproliferative neoplasms (cMPN), particularly Polycythemia Vera (PV).
STUDY RATIONALE	In recent years several reports have documented that histone deacetylases (HDACs) inhibitors induce neoplastic cells to undergo growth arrest, differentiation and/or apoptotic cell death. Among these agents, Givinostat (ITF2357) has most recently demonstrated effects on haematological parameters as well as constitutional parameters in patients with 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 can be expected with increased doses of Givinostat. Since the MTD of Givinostat has not been defined previously, the first aim of the current study is, therefore, to determine the maximum tolerated dose 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 Maximum Tolerated Dose (MTD) of Givinostat. The second aim of this study is to characterize the clinical efficacy of Givinostat at the MTD.
PRIMARY OBJECTIVES	***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. • To determine the safety and tolerability of Givinostat at the MTD ***after 3 cycles***.

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. • 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. • To determine the safety and tolerability of Givinostat at the MTD ***after 6 cycles***. • To characterize PK.
EXPLORATORY OBJECTIVES	***Parts A*** and ***B*** • To evaluate the effect of Givinostat on single parameters of the clinico-haematological ELN response criteria. • 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 the "**new**" ELN response criteria (i.e. the **revised** ELN response criteria).
PRIMARY ENDPOINTS	***Part A*** • Safety and tolerability evaluated as following: - 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). • Determination of the MTD of Givinostat based on cycle 1 DLT's.

	Part B • Overall response rate - i.e. Complete Response (CR) and Partial Response (PR) - of Givinostat at the MTD ***after 3 cycles***; the response will be evaluated according to the clinico-haematological ELN response criteria. • Safety and tolerability of Givinostat at the MTD ***after 3 cycles*** evaluated as following: - Number of patients experiencing adverse events; - Type, incidence, and severity of treatment-related adverse events, graded according to CTCAE v. 4.03.
SECONDARY ENDPOINTS	***Part A*** • Overall response rate - i.e. Complete Response (CR) and Partial Response (PR) - of Givinostat at the MTD ***after 3 and 6 cycles***; the response will be evaluated according to the clinico-haematological ELN response criteria. • Individual Givinostat concentrations tabulated by dose cohort along with descriptive statistics. ***Part B*** • Overall response rate - i.e. Complete Response (CR) and Partial Response (PR) - of Givinostat at the MTD ***after 6 cycles***; the response will be evaluated according to the clinico-haematological ELN response criteria. • Safety and tolerability of Givinostat at the MTD ***after 6 cycles*** evaluated as following: - Number of patients experiencing adverse events; - Type, incidence, and severity of treatment-related adverse events, graded according to CTCAE v. 4.03. • Individual Givinostat concentrations tabulated with descriptive statistics.
EXPLORATORY ENDPOINTS	***Part A*** and ***Part B*** • To evaluate the effect of Givinostat on each single response parameter according to the clinico-haematological ELN response criteria. • To evaluate the effects of Givinostat on PD markers by mRNA analysis. • To evaluate the effects of Givinostat on spleen size (by MRI or CT scan) in patients with confirmed splenomegaly at baseline. • Improvement of constitutional symptoms evaluated according to MPN-SAF QOL questionnaire. • Reduction of the $JAK2^{V617F}$ allele burden, tested by quantitative RT-PCR.

	• Reduction of the symptomatic treatment of pruritus in term of dosage and/or days of treatment. ***Part B*** • Overall response rate - i.e. Complete Remission and Partial Remission - of Givinostat at the MTD ***after 6 cycles***; the response will be evaluated according to the "**new**" ELN response criteria (i.e. the **revised** ELN response criteria). • To evaluate the effect of Givinostat on each single response parameter according to the "**new**" ELN response criteria (i.e. the **revised** ELN response criteria).
STUDY DESIGN	Two-part, multicenter, open label, non-randomized, phase Ib/II study.
NUMBER OF PATIENTS	About 52 evaluable patients, approximately 24 in ***Part A*** and 28 in ***Part B***.
TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION	Givinostat is a histone-deacetylases inhibitor. The product will be supplied as hard gelatine capsules for oral administration at the strength of 50 mg and/or 75 mg and/or 100 mg each. In ***Part A*** patients will treated in Dose Levels (DLs) at the following 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, additionally DLs may be used to establish the MTD. In ***Part B*** patients will be treated at the MTD established in ***Part A***.
TREATMENT PLAN	This is a two-part, multicenter, 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 finding part while ***Part B*** is assessing the preliminary efficacy. Patients will be enrolled either in ***Part A*** or ***Part B*** and transition from one part to the other is not allowed. Eligible patients for this study will have a confirmed diagnosis of PV according to the revised WHO criteria and the $JAK2^{V617}$ 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 may be expanded to all patients with cMPN.

Study therapy will be administered in 28 day cycles (4 weeks of treatment).

Disease response will be evaluated according to the ELN criteria 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 will **not** be 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 will be allowed to continue treatment with Givinostat (at the same dose and schedule) in a long-term study (Study N.: DSC/11/2357/44), provided that the long-term study has already received all necessary approvals in that specific country and site, and the study has been already initiated in that particular site.

Safety will be monitored at each visit throughout the entire duration of the study. Treatment will be administered on an outpatient basis and patients will be followed regularly with physical and laboratory tests, as specified in the protocol; in case of hospitalization, the treatment will be continued or interrupted according to the Investigators' decision.

Part A

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

Approximately 24 patients will be enrolled in this part of the study.

In ***Part A***, Dose Limiting Toxicity (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 will be graded according to CTCAE v. 4.03.

Dose escalation will be conducted according to a standard 3+3 design,

adopting a modified Fibonacci escalation schema. Patients will be enrolled in cohorts of 3 new patients (up to a maximum of 6) in rising dose levels.

Givinostat daily dose	**Givinostat dose level (DL)**	**DL used primarily to asses**
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.) has been previously shown to be well tolerated in several disorders and also in cMPN patients (Study N. DSC/07/2357/28 and Study N. DSC/08/2357/38). 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, additionally DLs may be introduced to more accurately define the MTD.

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) have been treated for 1 cycle, tolerability data will be evaluated and a decision to escalate to the next dose will be made.

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

At any time, if ≥ 2/3 or ≥ 2/6 patients at a given dose level develop a DLT, it is acceptable to de-escalate to an intermediate, not previously studied dose, 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 will start at the next lower dose below where ≥ 2/3 or ≥ 2/6 DLTs were observed (i.e. the MTD dose level).

If 2 or more patients per dose level experience a DLT, dose escalation will terminate and the MTD is the next lower dose level if no more than one out of 6 patients had a DLT at that level. Once all patients enrolled in ***Part A*** have been treated for at least 1 cycle, the study team will 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 will be permitted prior to determining the MTD. At that time, patients on treatment at lower dose levels may be allowed to escalate their Givinostat dose up to the MTD the remainder of the study (***Part A***) at the discretion of the Investigator **and** after the written authorization of Italfarmaco S.p.A.. Of note, patients initially dosed at lower dose levels that are allowed to escalate their Givinostat dose up to the MTD for the remainder part of the study (***Part A***), will follow the dose modification rules of ***Part B***. Only PV patients from ***Part A*** assigned to the dose selected for ***Part B*** (MTD) may be counted towards the efficacy assessment in ***Part B***. ***Part B*** ***Part B*** is a multicenter, 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. Approximately twenty eight patients will be enrolled in ***Part B*** at the MTD defined in ***Part A***, according to an optimized Simon's 2-stage design. The dose of Givinostat will be modified for protocol specified toxicities.
INCLUSION CRITERIA	1. Patients must be able to provide informed consent and be willing to sign an informed consent form; 2. Patients must have an age ≥18 years; 3. Patients must have a confirmed diagnosis of PV according to the revised WHO criteria; 4. Patients must have $JAK2^{V617F}$ positive disease; 5. Patients must have an **active/not controlled disease** defined as a) HCT ≥ 45% ***or*** HCT <45% in need of phlebotomy, **and** b) PLT counts > 400 $x10^9$/L, **and** c) WBC > 10 $x10^9$/L; 6. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 in ***Part A***, ECOG performance status ≤ 2 in ***Part B*** within 7 days of initiating study drug; 7. Female patient of childbearing potential has a negative serum or urine pregnancy test within 72 hours of the first dose of study therapy; please note that a borderline urine pregnancy test must be followed with a serum pregnancy test; 8. Use of an effective means of contraception for women of childbearing potential and men with partners of childbearing potential;

	9. Adequate and acceptable organ function within 7 days of initiating study drug; 10. Willingness and capability to comply with the requirements of the study. **Note that if the enrolment in *Part A* is slow (i.e. < 5 patients enrolled in 3 months), eligibility for this part of the study may be expanded to all patients with cMPN.** In this case, the inclusion criterion n. 5 will be modified as following only for ***Part A***: 5. Patients must have an **active/not controlled disease** defined as: a) ***ET patients:*** PLT counts > 600 x10^9/L; b) ***MF patients:*** no response according to EUMNET criteria. Note that an ***effective*** means of contraception for women of childbearing potential and men with partners of childbearing potential (i.e. inclusion criterion n. 5) is defined as following described based on different subject subgroups: **A.** ***Female subjects of childbearing potential:*** acceptable non-hormonal, contraceptive methods must be used from the 28 days before first dose of study drug through 3 months after the last dose of study drug and include the following: • True abstinence (absence of any sexual intercourse), when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. • Double barrier contraception such as diaphragm or a barrier method of contraception in conjunction with spermicidal jelly such as for example cervical cap with spermicide jelly and the male partner must use a condom with spermicide. • 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 a negative sperm post-vasectomy semen analysis) at least 6 months previously and 1 additional acceptable contraception method. **B.** ***Female subjects of non-childbearing potential*** must meet at least 1 of the following criteria: • Postmenopausal: Female subjects, less than 60 years of age, who have been amenorrheic for at least 2 years and have a

	serum FSH level within the laboratory's reference range for postmenopausal females. Female subject who are 60 years of age or older who are amenorrheic for greater than 2 years will be assume to be postmenopausal. • Documented hysterectomy or bilateral oophorectomy or both all other female subjects (including subjects with tubal ligations and subjects that do not have a documented hysterectomy) will be considered to be of childbearing potential. **C.** ***Male Subjects***, acceptable contraceptive methods must be used from Screening Visit through 3 months after the last dose of study drug, and include the following: • True abstinence (absence of any sexual intercourse), when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. • Condom with spermicide and the female partner must use an acceptable method of contraception, such as an oral, transdermal, injectable or implanted steroid-based contraceptive, or a diaphragm or a barrier method of contraception in conjunction with spermicidal jelly such as for example cervical cap with spermicide jelly. • Vasectomy (with a negative sperm post-vasectomy semen analysis) at least 6 months previously and 1 additional acceptable contraception method. • Male subjects must not donate sperm from the Screening Visit through 3 months after the last dose of study drug. Note also that – Male condom cannot be used with female condom due to risk of tearing. – The use of birth-control methods does not apply if the female partner has a bilateral oophorectomy, hysterectomy, or is postmenopausal (as defined above).
EXCLUSION CRITERIA	1. Active bacterial or mycotic infection requiring antimicrobial treatment; 2. Pregnancy or nursing; 3. A clinically significant QTc prolongation at baseline (e.g. repeated demonstration of a QTc interval ≥ 450 msec); 4. Use of concomitant medications known to prolong the QT/QTc interval; 5. Clinically significant cardiovascular disease including:

	a) Uncontrolled hypertension despite medical treatment, myocardial infarction, unstable angina within 6 months from study start; b) New York Heart Association (NYHA) Grade II or greater congestive heart failure; c) History of any cardiac arrhythmia requiring medication (irrespective of its severity); d) A history of additional risk factors for TdP (e.g. heart failure, hypokalemia, family history of Long QT Syndrome); 6. Known positivity for HIV; 7. Known active HBV and/or HCV infection; 8. Platelet count < 100 x 10^9/L within 14 days before enrolment (i.e. the receipt of the Patient ID); 9. Absolute neutrophil count < 1.2 x 10^9/L within 14 days before enrolment (i.e. the receipt of the Patient ID); 10. Serum creatinine > 2 x ULN; 11. Total serum bilirubin > 1.5 x ULN except in case of Gilbert's disease; 12. Serum aspartate aminotransferase/alanine aminotransferase (AST/ALT) > 3 x ULN; 13. History of other diseases (including active tumours), metabolic dysfunctions, physical examination findings, or clinical laboratory findings giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk from treatment complications; 14. Prior treatment with a JAK2 or HDAC inhibitor or participation in an interventional clinical trial for cMPN, including PV, ET or MF; 15. Systemic treatment for cMPN other than aspirin/cardio aspirin; 16. Hydroxyurea within 28 days before enrolment (i.e. the receipt of the Patient ID); 17. Interferon alpha within 14 days before enrolment (i.e. the receipt of the Patient ID); 18. Anagrelide within 7 days before enrolment (i.e. the receipt of the Patient ID); 19. Any other investigational drug or device within 28 days before enrolment (i.e. the receipt of the Patient ID); 20. Patient with known hypersensitivity to the components of study therapy.

	Of note, a ***repeated*** demonstration of a QTc interval ≥ 450 msec (i.e. exclusion criterion n. 3) means that, if the first ECG evaluation demonstrates 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) must be performed. The averaged value of these three ECG evaluations has to be used for the evaluation of the QTc interval requested by the exclusion criterion n. 3. In the CRF all the performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*. Note that an ***any other investigational drug or device*** (i.e. exclusion criterion n. 19) includes any investigational drug or device not already mentioned and detailed in the exclusion criteria n. 14, 15, 16 17 and/or 18.
DURATION OF TREATMENT	The study (both ***Part A*** and ***Part B***) will last up to a maximum of 24 weeks of treatment. However, after completion of the trial, all patients achieving clinical benefit will be allowed to continue treatment with Givinostat (at the same dose and schedule) in a long-term study (Study N.: DSC/11/2357/44), provided that the long-term study has already received all necessary approvals in that specific country and site, and the study has been already initiated in that particular site.
CONCOMITANT TREATMENT	Patients must **NOT** receive the following treatments during the study: a) Other investigational drugs while on this study; b) Cytotoxic agents, interferons or other approved treatment for cMPN other than aspirin/cardio-aspirin; c) Any drug known to provoke TdP. Other concomitant medications (e.g. symptomatic treatment of pruritus) and significant non-drug therapy (e.g. phlebotomy, blood transfusion) are permitted.
CRITERIA FOR RESPONSE	***Criteria for assessing clinico-haematological improvement*** Disease response will be evaluated according to the following clinico-haematological ELN criteria ***after 3 and 6 cycles*** of treatment with Givinostat both in ***Part A*** (secondary endpoints) and in ***Part B*** (primary and secondary endpoints, respectively). • ***Complete response***: 1. HCT<45% without phlebotomy, **and** 2. platelets ≤ 400 x10^9/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. As an exploratory endpoint, disease response will be 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***. • ***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 hemorrhagic 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 hemorrhagic 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. the **revised** ELN response criteria): 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. 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 will be evaluated according to the ELN and EUMNET criteria after 3 and 6 cycles of treatment with Givinostat, in ET and MF patients, respectively. **For ET** (from the clinico-hematological 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. In all cases, both for PV and ET patients, all phlebotomies performed in the first 3 weeks of treatment will **not** be 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 anaemia*: Increase of Hb ≥ 2 g/dL (but Hb < 12 g/dL) for non-RBC transfusion –dependent patients; or reduction ≥ 50% of transfusion requirement for RBC transfusion-dependent patients.
  2. *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.
  3. *Partial response in platelet count:* A ≥ 50% decrease in platelet count if baseline > 800 $x10^9$/L or platelet count increase by ≥ 50% x 10^9/L if baseline < 100 $x10^9$/L.
  4. *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
  5. *Progression in anaemia:* A hemoglobin decrease of ≥ 2 g/dL **or** a 50% increase in transfusion requirement **or** becoming transfusion dependent
  6. *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. 7. *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 will be evaluated directly by patients according to MPN-SAF QOL questionnaire. ***Criteria for determination of MTD*** Once all patients enrolled in ***Part A*** have been treated for at least 1 cycle, the study team will 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 will be permitted prior to determining the MTD. At that time, patients on treatment at lower dose levels may 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 written authorization of Italfarmaco S.p.A.. Of note, patients initially dosed at lower dose levels that are allowed to escalate their Givinostat dose up to the MTD for the remainder part of the study (***Part A***), will follow the dose modification rules of ***Part B.*** ***Criteria for characterization of PK*** Plasma concentrations from ***Parts A*** and ***B*** will be evaluated by dose and time point for all patients and time points with at least 1 PK assessment.
DOSE MODIFICATIONS RULES, TREATMENT INTERRUPTION AND TREATMENT DISCONTINUATION	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. **Dose modification criteria in *Part A*** 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. The first dose

	modification should be one dose level below the current dose, the second modification should be two dose levels below. Study drug may be resumed at lower dose level once the event resolves to at least grade 1 or baseline values. If toxicities meeting modification criteria occur after the second dose reduction, therapy must be discontinued. Patients with unresolved toxicities **lasting 2 weeks or longer** will not be permitted to continue on study. Patients experiencing Grade 3 or 4 unmanageable toxicity will require immediate dose interruption and notification to the Sponsor. Treatment for each new cycle will be delayed until dose limiting toxicities that are clearly not related to disease progression have resolved to at least Grade 1 or the patient's baseline. **Dose modification criteria in *Part B*** Dose adjustments are permitted for patients who do not tolerate the protocol-specified dosing schedule, in order to allow to these patients to continue the treatment with Givinostat. 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. 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). Each dose modification has to be recorded on the CRF. Patients initially dosed at lower dose levels in ***Part A*** that, after the definition of MTD, are 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 written authorization of Italfarmaco S.p.A., will follow the dose modifications criteria for ***Part B***. Total daily dose may never exceed the MTD defined in ***Part A*** (i.e. 100 mg b.i.d.). **Treatment interruption and treatment discontinuation in *Parts A* and *B*** In some circumstances, it may be necessary to temporarily interrupt treatment as a result of adverse experiences that may have an unclear relationship to study drug. Study drug may be withheld by the Investigator at any time if there is concern about patient safety and for all aspects of the conduct of the protocol, since the safety of the

	individual patient is paramount. Treating Investigator may employ any means necessary to ensure patient safety, particularly in medical circumstances not anticipated by this protocol. Dose adjustments are permitted for patients who do not tolerate the protocol-specified dosing schedule, in order to allow to these patients to continue the treatment with Givinostat. The objective of the Givinostat dose adjustment rules is to optimize the response for each individual patient, avoiding specific drug-related toxicities. If the patient inadvertently misses a drug dose, no additional trial medication should be taken that day or in the next days in the effort to replace the material that has been missed. If vomiting occurs, no additional trial medication should be taken that day in an effort to replace the material that has been vomited. If the study drug is interrupted for any reason for more than 4 weeks continuously, dosing may be not be restarted. Patients have the right to withdraw from the study at any time for any reason. The Investigator has the right to withdraw patients from the study due to medical reasons according to his/her discretion. If a pregnancy occurs, the patient will be replaced and another patient in that DL should be recruited. If the patient discontinues the study because of an adverse event whether or not drug related, he/she must be followed until resolution or stabilization of the event, whichever occurs first. In case of lack of compliance or in case the patient is found not eligible, the patient discontinuation have to be discussed between Investigator and Sponsor. If the patient discontinues for any reason (including discontinuation for pregnancy), with drug related adverse event ongoing at study end, he/she must be followed until resolution or stabilization of the event or until it is reasonable to consider the event not drug related any more or until the start of a new treatment, whichever occurs first. If the patient needs to take one of the concomitant medications included in list of "Drugs with risk of Torsades de Pointes", the treatment with Givinostat is to be promptly discontinued and the patient must leave the study. In case of multiple reasons (e.g. patient withdraws the consent for toxicity), "adverse events" should be indicated as the primary reason whenever applicable. All relevant information related to the reason for treatment discontinuation including contributory factors must be included on the 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. Should any drug-related AE still be ongoing beyond the last scheduled visit, this must be followed at subsequent follow-up visits until recovery. If a patient does not return for a scheduled visit, every

	effort should be made to contact the patient. In any circumstance every effort should 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 must be included on the CRF.
STATISTICAL METHODS	This is a two-part, multicenter, open label, non-randomized, phase Ib/II study. A standard 3+3 design adopting a modified Fibonacci escalation schema will be used in ***Part A***. Sample size for ***Part B*** was discussed for the primary endpoint defined as the Overall Response Rate after 3 cycles. A Simon's 2-stage design will be employed enrolling up to 28 patients in ***Part B*** with the aim of testing the "null hypothesis" that RR $\leq$ 0.50 versus the "alternative" that RR $\geq$ 0.75. Response rate will be assessed as defined in the Criteria for Response section. Overall up to 28 patients will need to be recruited, 12 patients being enrolled in Stage-1. Futility will be assessed after 12 patients enrolled (Stage 1). Please note that PV patients enrolled at the MTD in ***Part A*** may be counted towards Stage 1. Under the "null hypothesis" (if RR = 0.50), the expected total sample size is of 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 favour 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 respond to the treatment the trial will be terminated rejecting the "alternative" that RR $\geq$ 0.75. Otherwise, the trial goes on to Stage-2 enrolling further 16 patients to a total of 28 patients. If at the end of Stage-2, a total of 17 or fewer patients respond to the treatment the "alternative hypothesis" that RR $\geq$ 0.75 will be rejected; alternatively, if 18 or more patients respond, the "null hypothesis" that RR $\leq$ 0.50 will be rejected. Estimations are obtained from proprietary software (based on SAS ® 9.2) according to the algorithm proposed by R. Simon. Summary statistics will be calculated for all variables. For each continuous variable, the mean, standard deviation, median, minimum value and maximum value will be computed. For each discrete variable the number of patients in each category with non-missing values in relation to all patients with non-missing values of that variable will be provided. Results will be displayed within each cohort and overall, where applicable. Statistical calculations will be carried-out by resorting to SAS version 9.2 (or later). Both continuous and categorical data will be summarized and tabulated in 2-way tables (variable-by-visit). The main purpose of this phase Ib/II study consists in providing

	accurate estimates of clinically relevant variables and measures. From the statistical viewpoint this translates in estimating confidence intervals (CIs) with adequate precision where precision represents the degree of uncertainty. The two tailed 95% CIs of the sample estimates will be computed using parametric approaches if deemed appropriate. Otherwise the StatXact-4 software will be used in order to compute Exact/Nonparametric 95% CIs. Sub-groups analyses will be performed mainly for exploratory purposes. Since these analyses will be used to promote hypothesis rather than confirm them, no adjustment 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. The following analysis sets will be defined: - Safety analysis set (SAF): The Safety analysis set will include all recruited patients who receive at least one dose of study medication. All safety analyses will be conducted on this population. - 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. All efficacy analyses will be conducted on this population and they will be based on the *effective/actual* DL/daily doses of Givinostat at which each patient has been treated. - Per Protocol analysis set (PP): In order to assess the robustness of the efficacy analysis, the analysis of the efficacy endpoints could be repeated in 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. - MTD analysis set: The MTD analysis set will include all patients who experienced a DLT in Cycle 1 or received at least 90% of the doses of study medication in cycle 1. The first cycle data from this analysis set will be used to determine MTD. Patients who didn't experience a DLT and missed more than 10% of the doses in Cycle 1 of Part A will be replaced. - PK Analysis set: will consist of all SAF patients who with at least 1 PK assessment. This analysis set will be used for PK analysis. 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 the study. A listing of reasons of exclusion from analysis population will be provided.

	Italfarmaco S.p.A. will perform a preliminary analysis of data after the completion of the first cycle of treatment from all patients recruited in ***Part A***, in order to assess the MTD to be used for ***Part B***. Moreover, a preliminary analysis will be performed on the 12 patients of the stage I (***Part B***). If six or fewer responses will be observed during the first stage then the study will be stopped. If seven or more responses will be observed in stage I, further 16 patients will be enrolled in ***Part B***. In this case, a final statistical analysis will be performed considering all patients enrolled in the two study phases. In addition, Italfarmaco S.p.A. can perform a preliminary analysis of data in case of necessary safety and efficacy updates (e.g. to update regulatory documents and/or the drug safety profile, to revise the development program).

This study is registered in the EudraCT database and in Clinicaltrial.gov database.

1. INTRODUCTION

1.1 Medical indication and current treatments

Polycythemia Vera (PV), also termed Polycythemia rubra vera, together with Essential Thrombocythemia (ET) and Myelofibrosis (MF) belongs to a distinct group of Ph-chromosome-negative chronic myeloproliferative neoplasms (cMPN) characterized by clonal proliferation of multipotent haematopoietic stem cells leading to thrombocytosis, leukocytosis, erythrocytosis and bone marrow fibrosis [**1**, **2**]. PV is characterized by a tri-lineage expansion of morphologically normal red cells, white cells, and platelets [**3**]. Generally, in PV it is possible to recognise two phases: (a) an initial proliferative polycythaemic phase, associated with increased red cell mass, which results in an increased propensity to thromboembolic events leading to significant morbidity and mortality, and (b) a "spent", or post-polycythaemic phase, in which cytopenias, including anaemia, are associated with ineffective haematopoiesis, bone marrow fibrosis and hypersplenism. The course of the disease is associated with a tendency to transform to myelofibrosis and leukaemia, events which may be influenced by treatment [**4**].

In 2005 the acquired mutation of the JAK2 kinase ($JAK2^{V617F}$) was discovered in PV patients [**5**, **6**, **7**, **8**]. The JAK2 kinase, through its association with cytokine receptors and receptor tyrosine kinases, play a central role in cytokine signalling and signal transduction. The $JAK2^{V617F}$ mutation, that is present in about 90-95% of PV patients, results in expression of a constitutively activated JAK2 tyrosine kinase that confers growth factors independence and hypersensitivity to blood cell lines [**5**, **6**, **8**, **9**].

PV is diagnosed in asymptomatic patients during the routine blood cell count analysis or, more commonly, on the basis of skin and mucous membrane redness or splenomegaly. Pruritus (aquagenic or not), fatigue, headache, vision disturbances, paraesthesia, erythromelalgia (acral dysesthesia and erythema) are the most common disease symptoms, that are present in the majority of patients and often severely deteriorate their quality of life [**10**, **11**].

The long-term prognosis of PV patients is variable. Particularly without treatment, about half of the people who have PV with symptoms die in less than 2 years, while with treatment, median survival in PV is 15 years. The 10-year risk of developing either myelofibrosis (MF) or acute myeloid leukaemia (AML) is 10% and 6%, respectively. The primary causes of morbidity and mortality in PV patients are thrombosis, haematological transformation, and haemorrhage, responsible for 41%, 13% and 4% of deaths, respectively [**12**].

The first step in PV patient management is risk-stratification. The main two factors to be considered for risk-stratification are an age > 60 years and/or a history of thrombosis. Other factors, such as haematocrit, leukocytes and/or platelets counts and generic cardiovascular risk factors, are taken into account for risk stratification but their significance is still controversial.

In low risk patients, it is recommended to control the erythrocytosis by phlebotomy and, when no contraindication exists, to administer low-dose aspirin [**2**, **13**]. In patients with intermediate risk of thrombosis, phlebotomy should be offered to keep the haematocrit below appropriate values and in general it is recommended to add a low daily dose of aspirin. When platelet counts are > 1000 x 10^9/L, additional myelosuppressive treatment should be considered. High-risk PV patients require cytoreductive therapy, even if the first step in the disease management is always phlebotomy plus low-dose aspirin [**2**].

Standard front-line therapy for high risk PV is hydroxycarbamide (formerly known as hydroxyurea, HU), the first choice cytoreductive agent [**10**, **13**] authorised for PV therapy (both in Europe than in USA). Hydroxycarbamide is an antimetabolite that inhibits the enzyme ribonucleotide diphosphate reductase which has a rate-limiting role in DNA synthesis. It controls blood counts and reduces the rate of thromboembolic events. In general, hydroxycarbamide is well tolerated and has good clinical effect [**4**, **10**], but its use is burdened by a not negligible rate of neoplastic transformation of the disease [**14**, **15**].

In addition to hydroxycarbamide, PV patients can be also treated with alkylating agents (pipobroman and busulfan) authorised in Europe for treatment of PV. Pipobroman is a piperazine derivative and is available for clinical use in some European countries (France and Italy). The role of pipobroman in inducing the neoplastic transformation of PV has been recently emphasized as it appears to be even greater than that of hydroxycarbamide [**14**, **15**]. Busulphan has been reported to be effective in controlling blood counts in PV since the 50's, but an extensive use of the drug is limited by its leukemogenic potential [**4**, **16**]. In current clinical practice, pipobroman and busulfan are considered as second line therapies in hydroxycarbamide-intolerant or refractory cases [**2**].

Further to cytoreductive and anti-thrombotic therapy, very often patients are candidate to receive symptomatic treatments to control systemic symptoms, such as pruritus, headache, microvascular disturbances and fatigue, which can severely impair the patients' quality of life.

Recently, a JAK inhibitor was authorized both in Europe (i.e. Jakavi, INN: ruxolitinib) and in US (Jakafi, INN: ruxolitinib) for the treatment of adult patients with PV who are resistant to or intolerant of hydroxyurea.

The clinical course of PV and ET is marked by significant thrombotic complications and a variable risk to evolve into myelofibrosis and eventually to acute myeloid leukemia. Randomized clinical trials performed in USA and Europe have shown that cytoreductive treatment of blood hyperviscosity, chemotherapy and low-dose aspirin have dramatically reduced the number of thrombo-hemorrhagic episodes and substantially improved survival.

As compared to PV and ET, MF has the worst prognosis with a median survival or 3-5 years. A prognostic score system was developed where the presence of leukocytosis, leukopenia or anaemia was used to identify three groups of patients with different survival, from 1 to 8 years. Conventional therapies in this disease were palliative and include many drugs in addition to supportive therapy to improve anaemia, thrombocytopenia and progressive splenomegaly.

Recently, a JAK inhibitor was authorized for the treatment of disease-related splenomegaly or symptoms in adult patients with MF in Europe (i.e. Jakavi, INN: ruxolitinib) and to treat intermediate or high-risk MF patient in US (i.e. Jakafi, INN: ruxolitinib).

1.2 Rationale

Polycythemia Vera (PV) is a myeloproliferative disorder which is considered to be a clonal disease derived from a transformed pluripotent hematopoietic stem cell. This cell is thought to lead to overactive hematopoiesis, driven by a constitutively active JAK-STAT signalling pathway, caused by V617F mutations within exons 12 and 14 of the JAK2 gene [**17**]. The clinical course of PV is marked by significant thrombotic complications with an estimated incidence of 18x1000 person-years, accounting for 45% of all deaths; myelofibrosis and transformation into AML may occur in a small percentage of cases (5x1000 person-years) [**18**].

The mainstay of current therapy is aimed at reducing the number of these disease related complications by reducing blood hyperviscosity. Cytoreductive agents have been proven efficacious in this regard, but concerns regarding acceleration of disease transformation remain, thereby substantiating the need for novel therapies [**2**].

Recently, small molecule inhibitors of the JAK2 kinase have at least partially validated the importance of this molecule in the clinical setting and several JAK2 inhibitors are currently under clinical development in PV. Recently, a JAK inhibitor was authorized both in Europe (i.e. Jakavi, INN: ruxolitinib) and in US (Jakafi, INN: ruxolitinib) for the treatment of adult patients with PV who are resistant to or intolerant of hydroxyurea.

Histone deacetylases (HDACs) are enzymes involved in the remodelling of chromatin and play a key role in the epigenetic regulation of gene expression.

Givinostat (ITF2357) is a potent, orally available small molecule inhibitor of HDACs and it has shown to interfere with the JAK/STAT signalling pathway in preclinical studies.

1.3 Preclinical rationale

Completed and updated data following described are reported in the Section 5 "Non-clinical studies" of the current Investigator Brochure Dossier related to ITF2357.

Givinostat has an anti-proliferative effect for tumor cells. Its efficacy in hematological tumors bearing the $JAK2^{V617F}$ mutation is remarkable, showing an IC50 of 95 nM for SET-2 and 175 nM for HEL cell lines which are hetero- and homozygous for the mutant protein, respectively. These values are two- to three-fold lower than the ones observed for a JAK2 wild type tumor cell such as the erythroleukemic cell line K562, for which the IC50 is 350 nM [**19**, **20**]. Combination benefit of Givinostat and hydroxyurea was observed in *in-vitro* cytotoxicity assays conducted in HEL and UKE cells.

1.4 Clinical studies

Completed and updated data following described are reported in the Section 6 "Effects in humans" of the current Investigator Brochure Dossier related to ITF2357.

Givinostat has been tested in a number of clinical studies. Three major indications have been explored with Givinostat, inflammatory disease, neuromuscular disorders and oncology. The most common AEs observed were thrombocytopenia as well as gastrointestinal toxicities. AEs were generally mild to moderate and reversible upon discontinuation of study drug. The maximum administered dose was a single dose of 600 mg in healthy volunteers and up to 400 mg once per week in patients with multiple myeloma. Doses up to approximately 100 mg b.i.d. were generally very well tolerated. At higher doses of Givinostat transient reduces haematological parameters (particularly platelets) and diarrhoea as well as nausea and vomiting were observed.

1.4.1 Givinostat in chronic myeloproliferative neoplasms

Givinostat is an HDACi and, as such, it has been investigated for its inhibitory activity on the autonomous proliferation of cells obtained by PV and ET patients carrying the $JAK2^{V617F}$ mutation and to elucidate the mechanism of action of this inhibition. Cells obtained from PV or ET patients carrying the $JAK2^{V617F}$ mutation are sensitive in colony assays to a 100-500 lower dose of Givinostat as compared to cells bearing un-mutated JAK2. Moreover, Givinostat promotes the outgrowth of normal colonies over that of $JAK2^{V617F}$ mutated cells *in vitro* and induces down-modulation of the $JAK2^{V617F}$ but not JAK2 wild type protein. $JAK2^{V617F}$ inhibition by Givinostat takes place at the post-transcriptional level and is followed by down-modulation of the phosphorylated STAT5 protein and PRV-1 gene expression.

Two phase II study were conducted in patients with $JAK2^{V617F}$ positive cMPN. A phase II of Givinostat monotherapy, was completed with positive results in patients with $JAK2^{V617F}$ positive PV, ET and MF (Study N.: DSC/07/2357/28) [**22**]. Another phase II study combining Givinostat with hydroxyurea, was recently completed with positive results in patients with $JAK2^{V617F}$ positive PV not responding to the maximum tolerated dose of hydroxyurea monotherapy (Study N. DSC/08/2357/38); a total of 44 PV patients received Givinostat doses of either 50 or 100 mg per day and were treated for up to 24 weeks [**23**]. The ELN response criteria [**21**] were used to assess the primary endpoint after 12 weeks of treatment. Complete or partial responses were observed in approximately 50% of patients across both dose levels.

At the time being, a multicenter, open label, long-term study testing the long term safety, tolerability and efficacy of Givinostat in patients with cMPN following core protocols and/or patient-named compassionate use program is ongoing (Study N. DSC/11/2357/44).

After completion of this current trial (Study N. DSC/12/2357/45), all patients achieving clinical benefit will be allowed to continue treatment with Givinostat (at the same dose and schedule) in the above mentioned long-term study (Study N.: DSC/11/2357/44),

provided that the long-term study has already received all necessary approvals in that specific country and site and the study was initiated in that particular site.

1.5 Rationale for a phase Ib/II study

Preliminary signs of clinical activity in patients with JAK2 mutant cMPN as described above, have been observed in two studies with Givinostat. 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 can be expected with increased doses of Givinostat.

Since the MTD of Givinostat has not been defined previously, the first aim of the current study is therefore, to determine the maximum tolerated dose 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 Maximum Tolerated Dose (MTD) of Givinostat. The second aim of this study is to characterize the clinical efficacy of Givinostat at the MTD.

2. STUDY OBJECTIVES

2.1 Primary objectives

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 [**21**] (see paragraph 4.6.1).
- 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 [**21**] (see paragraph 4.6.1).
- 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 [**21**] (see paragraph 4.6.1).
- To determine the safety and tolerability of Givinostat at the MTD ***after 6 cycles***.
- To characterize PK.

2.3 Exploratory objectives

Parts A and ***B***

- To evaluate the effect of Givinostat on single parameters of the clinico-haematological ELN response criteria [**21**] (see paragraph 4.6.1).
- 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) [**33**] (see paragraph 4.8.7).
- To evaluate the effect of Givinostat on single parameters of the "**new**" ELN response criteria (i.e. the **revised** ELN response criteria) [**33**] (see paragraph 4.8.7).

3. STUDY ENDPOINTS

3.1 Primary endpoints

Part A

- Safety and tolerability evaluated as following:
  - 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).
- Determination of the MTD of Givinostat based on cycle 1 DLT's.

Part B

- Overall response rate - i.e. Complete Response (CR) and Partial Response (PR) - of Givinostat at the MTD ***after 3 cycles***; the response will be evaluated according to the clinico-haematological ELN response criteria [**21**] (see paragraph 4.6.1).
- Safety and tolerability of Givinostat at the MTD ***after 3 cycles*** evaluated as following:
  - Number of patients experiencing adverse events;
  - Type, incidence, and severity of treatment-related adverse events, graded according to CTCAE v. 4.03.

3.2 Secondary endpoints

Part A

- Overall response rate - i.e. Complete Response (CR) and Partial Response (PR) - of Givinostat at the MTD ***after 3 and 6 cycles***; the response will be evaluated according to the clinico-haematological ELN response criteria [**21**] (see paragraph 4.6.1).
- Individual Givinostat concentrations tabulated by dose cohort along with descriptive statistics.

Part B

- Overall response rate - i.e. Complete Response (CR) and Partial Response (PR) - of Givinostat at the MTD ***after 6 cycles***; the response will be evaluated according to the clinico-haematological ELN response criteria [**21**] (see paragraph 4.6.1).

- Safety and tolerability of Givinostat at the MTD ***after 6 cycles*** evaluated as following:
  - Number of patients experiencing adverse events;
  - Type, incidence, and severity of treatment-related adverse events, graded according to CTCAE v. 4.03.
- Individual Givinostat concentrations tabulated with descriptive statistics.

3.3 Exploratory endpoints

Part A and ***Part B***

- To evaluate the effect of Givinostat on each single response parameter according to the clinico-haematological ELN response criteria [**21**] (see paragraph 4.6.1).
- To evaluate the effects of Givinostat on PD markers by mRNA analysis.

- To evaluate the effects of Givinostat on spleen size (by MRI or CT scan) in patients with confirmed splenomegaly at baseline.
- Improvement of constitutional symptoms evaluated according to MPN-SAF QOL questionnaire [**24, 32**].
- Reduction of the $JAK2^{V617F}$ allele burden, tested by quantitative RT-PCR.
- Reduction of the symptomatic treatment of pruritus in term of dosage and/or days of treatment.

Part B

- Overall response rate - i.e. Complete Remission and Partial Remission - of Givinostat at the MTD ***after 6 cycles***; the response will be evaluated according to the "**new**" ELN response criteria (i.e. the **revised** ELN response criteria [**33**], see paragraph 4.8.7).
- To evaluate the effect of Givinostat on each single response parameter according to the "**new**" ELN response criteria (i.e. the **revised** ELN response criteria [**33**], see paragraph 4.8.7).

4. INVESTIGATIONAL PLAN

4.1 Overall study design

This is a two-part, multicenter, 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*** will commence where the preliminary efficacy of Givinostat in PV patients will be established. Patients will be 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) may be **counted** towards the efficacy assessment in ***Part B***.

Eligible patients for this study will 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 may 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 will be a combination of his/her site ID, study part ID and patient screening number, e.g. IT01-A01) will be assigned to each patient and it will identify the patient within his/her enrolment confirmation by Italfarmaco S.p.A. or its designee and never be reused in case of screening failure. After the enrolment confirmation and the assignation of the dose level before the first drug intake, a unique patient identification code (i.e. **patient ID** which will be a combination of patient screening number ID and dose level ID, e.g. IT01-A01-DL1) will be assigned to each patient and it will identify the patient

throughout his/her participation in the study and never be reused in case of premature drop-out.

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

Disease response will be evaluated according to the clinico-haematological ELN criteria [**21**] 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 will **not** be 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 will be allowed to continue treatment with Givinostat (at the same dose and schedule) in a long-term study (Study N.: DSC/11/2357/44), provided that the long-term study has already received all necessary approvals in that specific country and site, and the study has been already initiated in that particular site.

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

4.1.1 *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.

Approximately 24 patients will be enrolled in ***Part A***.

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

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

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

4.1.1.1 Definition of Dose Limiting Toxicity (DLT)

Dose Limiting Toxicity (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 will be graded according to NCI Common Terminology Criteria for AE (CTCAE v. 4.03, 14th June 2010).
Only Dose Limiting Toxicities (DLTs) experienced during the first cycle of treatment will be 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*** will be replaced (see paragraph 4.6.4).

4.1.1.2 Study team definition

The study team will include: selected Principal Investigator/s (i.e. Chairman and/or Principal Investigator/s who recruited the patients under discussion), the CRO Medical Monitor, Italfarmaco Medical Expert/s, Italfarmaco Clinical Scientist and any other additional personnel, *if necessary*.

4.1.1.3 Dose Levels (DLs) and dose escalation scheme

Dose escalation will be conducted according to a standard 3+3 design, adopting a modified Fibonacci escalation schema [**25**, **26**, **27**]. Patients will be 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 has been followed for a minimum of 1 cycle after the first administration of study agent, and the current dose has been determined to have an acceptable safety profile according to the following rules summarized 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 asses
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.) has been previously shown to be well tolerated in studies (Section 6 "Effects in humans" of the current 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 DL 5) before assigning patients to DL0.

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

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

4.1.1.4 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) have been treated for 1 cycle, tolerability data will be evaluated and a decision to escalate to the next dose will be made.

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

At any time, if ≥ 2/3 or ≥ 2/6 patients at a given dose level 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 will start at the next lower dose below where ≥ 2/3 or ≥ 2/6 DLTs were observed (i.e. the MTD dose level).

4.1.1.5 Definition of MTD

If 2 or more patients per dose level experience a DLT, dose escalation will terminate and the MTD is the next lower dose level if no more than one out of 6 patients had a DLT at that level. Once all patients enrolled in ***Part A*** have been treated for at least 1 cycle, the study team will 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 will be permitted prior to determining the MTD.

At that time, patients on treatment at lower dose levels may 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 written authorization of Italfarmaco S.p.A.. Of note, patients initially dosed at lower dose levels that are allowed to escalate their Givinostat dose up to the MTD for the remainder part of the study (***Part A***), will follow the dose modification rules of ***Part B*** (see paragraph 4.3.3.2). Total daily dose may never exceed the MTD defined in ***Part A*** (i.e. 100 mg b.i.d.).

4.1.2 *Part B*

Part B is a multicenter, 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.

Approximately twenty eight patients will be enrolled in ***Part B*** starting at the MTD defined in ***Part A*** (i.e. 100 mg b.i.d.), according to an optimized Simon's 2-stage design [**30**].

The dose of Givinostat will be modified for protocol specified toxicities (see paragraph 4.3.3.2).

4.2 Trial organization

The conduct of this study will be committed to a Contract Research Organization (CRO). In any case, Italfarmaco S.p.A. remains responsible for the development, writing and finalization of the study protocol, the investigational medicinal product (IMP) production and the Pharmacovigilance activities.

For all study activities, with the exception above mentioned, the designated CRO or their delegates (e.g. a Contact Manufacturing Organization (CMO) delegated for the IMP secondary packaging and management) can apply internal standard operating procedures (SOPs).

Trial activities will be supervised by Italfarmaco S.p.A. through regular contacts with the staff of the designated CRO or their delegates and/or Investigators, *as necessary*.

4.3 Patient population

The study will include patients of both genders with an established diagnosis of $JAK2^{V617F}$ Polycythemia Vera according to the revised WHO criteria, who have an active and/or not controlled disease.

In case of slow recruitment the Sponsor may decide to expand the population to patients with cMPN positive to $JAK2^{V617F}$.

4.3.1 Inclusion criteria

Patients must meet the following criteria to be eligible for study entry:

1. Patients must be able to provide informed consent through the signature of an informed consent form;
2. Patients must have an age ≥18 years;
3. Patients must have a confirmed diagnosis of PV according to the revised WHO criteria;
4. Patients must have $JAK2^{V617F}$ positive disease;
5. Patients must have an **active/not controlled disease** defined as
   a) HCT ≥ 45% ***or*** HCT <45% in need of phlebotomy, **and**
   b) PLT counts > 400 $x10^9$/L, **and**
   c) WBC > 10 $x10^9$/L;
6. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status [**28**] ≤ 1 in ***Part A***, ECOG performance status ≤ 2 in ***Part B***, within 7 days of initiating study drug;
7. Female patient of childbearing potential has a negative serum or urine pregnancy test within 72 hours of the first dose of study therapy; please note that a borderline urine pregnancy test must be followed with a serum pregnancy test;
8. Use of an ***effective*** means of contraception for women of childbearing potential and men with partners of childbearing potential;
9. Adequate and acceptable organ function within 7 days of initiating study drug;
10. Willingness and capability to comply with the requirements of the study.

Note that if the enrolment in *Part A* is slow (i.e. < 5 patients enrolled in 3 months), eligibility for this part of the study may be expanded to all patients with cMPN. In this case, the inclusion criterion n. 5 will be modified as following only for ***Part A***:

5. Patients must have an **active/not controlled disease** defined as:
   a) ***ET patients:*** PLT counts > 600 $x10^9$/L;
   b) ***MF patients:*** no response according to EUMNET criteria [**29**].

Note that an ***effective*** means of contraception for women of childbearing potential and men with partners of childbearing potential (i.e. inclusion criterion n. 5) is defined as following described based on different subject subgroups:

A. ***Female subjects of childbearing potential:*** acceptable non-hormonal, contraceptive methods must be used from the 28 days before first dose of study drug through 3 months after the last dose of study drug and include the following:

- True abstinence (absence of any sexual intercourse), when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

- Double barrier contraception such as diaphragm or a barrier method of contraception in conjunction with spermicidal jelly such as for example cervical cap with spermicide jelly and the male partner must use a condom with spermicide.
- 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 a negative sperm post-vasectomy semen analysis) at least 6 months previously and 1 additional acceptable contraception method.

B. ***Female subjects of non-childbearing potential*** must meet at least 1 of the following criteria:

- Postmenopausal: Female subjects, less than 60 years of age, who have been amenorrheic for at least 2 years and have a serum FSH level within the laboratory's reference range for postmenopausal females. Female subject who are 60 years of age or older who are amenorrheic for greater than 2 years will be assume to be postmenopausal.
- Documented hysterectomy or bilateral oophorectomy or both all other female subjects (including subjects with tubal ligations and subjects that do not have a documented hysterectomy) will be considered to be of childbearing potential.

C. ***Male Subjects***, acceptable contraceptive methods must be used from Screening Visit through 3 months after the last dose of study drug, and include the following:

- True abstinence (absence of any sexual intercourse), when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
- Condom with spermicide and the female partner must use an acceptable method of contraception, such as an oral, transdermal, injectable or implanted steroid-based contraceptive, or a diaphragm or a barrier method of contraception in conjunction with spermicidal jelly such as for example cervical cap with spermicide jelly.
- Vasectomy (with a negative sperm post-vasectomy semen analysis) at least 6 months previously and 1 additional acceptable contraception method.
- Male subjects must not donate sperm from the Screening Visit through 3 months after the last dose of study drug.

Note also that

- Male condom cannot be used with female condom due to risk of tearing.
- The use of birth-control methods does not apply if the female partner has a bilateral oophorectomy, hysterectomy, or is postmenopausal (as defined above).

4.3.2 Exclusion criteria

Patients must **NOT** meet any of the following criteria to be eligible for study entry:

1. Active bacterial or mycotic infection requiring antimicrobial treatment;
2. Pregnancy or nursing;
3. A clinically significant QTc prolongation at baseline (e.g. repeated demonstration of a QTc interval ≥ 450 msec);
4. Use of concomitant medications known to prolong the QT/QTc interval;
5. Clinically significant cardiovascular disease including:
   a) Uncontrolled hypertension despite medical treatment, myocardial infarction, unstable angina within 6 months from study start;
   b) New York Heart Association (NYHA) Grade II or greater congestive heart failure;
   c) History of any cardiac arrhythmia requiring medication (irrespective of its severity);
   d) A history of additional risk factors for TdP (e.g. heart failure, hypokalemia, family history of Long QT Syndrome);
6. Known positivity for HIV;
7. Known active HBV and/or HCV infection;
8. Platelet count < 100 $x10^9$/L within 14 days before enrolment (i.e. the receipt of the Patient ID);
9. Absolute neutrophil count < 1.2 $x10^9$/L within 14 days before enrolment (i.e. the receipt of the Patient ID);
10. Serum creatinine > 2 x ULN;
11. Total serum bilirubin > 1.5 x ULN except in case of Gilbert's disease;
12. Serum aspartate aminotransferase/alanine aminotransferase (AST/ALT) > 3 x ULN;
13. History of other diseases (including active tumours), metabolic dysfunctions, physical examination findings, or clinical laboratory findings giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk from treatment complications;
14. Prior treatment with a JAK2 or HDAC inhibitor or participation in an interventional clinical trial for cMPN, including PV, ET or MF;
15. Systemic treatment for cMPN other than aspirin/cardio aspirin;
16. Hydroxyurea within 28 days before enrolment (i.e. the receipt of the Patient ID);
17. Interferon alpha within 14 days before enrolment (i.e. the receipt of the Patient ID);
18. Anagrelide within 7 days before enrolment (i.e. the receipt of the Patient ID)
19. Any other investigational drug or device within 28 days before enrolment (i.e. the receipt of the Patient ID);
20. Patient with known hypersensitivity to the components of study therapy.

Of note, a ***repeated*** demonstration of a QTc interval ≥ 450 msec (i.e. exclusion criterion n. 3) means that, if the first ECG evaluation demonstrates 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) must be performed. The averaged value of these three ECG evaluations has to be used for the evaluation of the QTc interval requested by the exclusion criterion n. 3. In the CRF all the performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*.

Note that an ***any other investigational drug or device*** (i.e. exclusion criterion n. 19) includes any investigational drug or device not already mentioned and detailed in the exclusion criteria n. 14, 15, 16 17 and/or 18.

4.3.3 Criteria for dose modifications, treatment interruption and treatment discontinuation

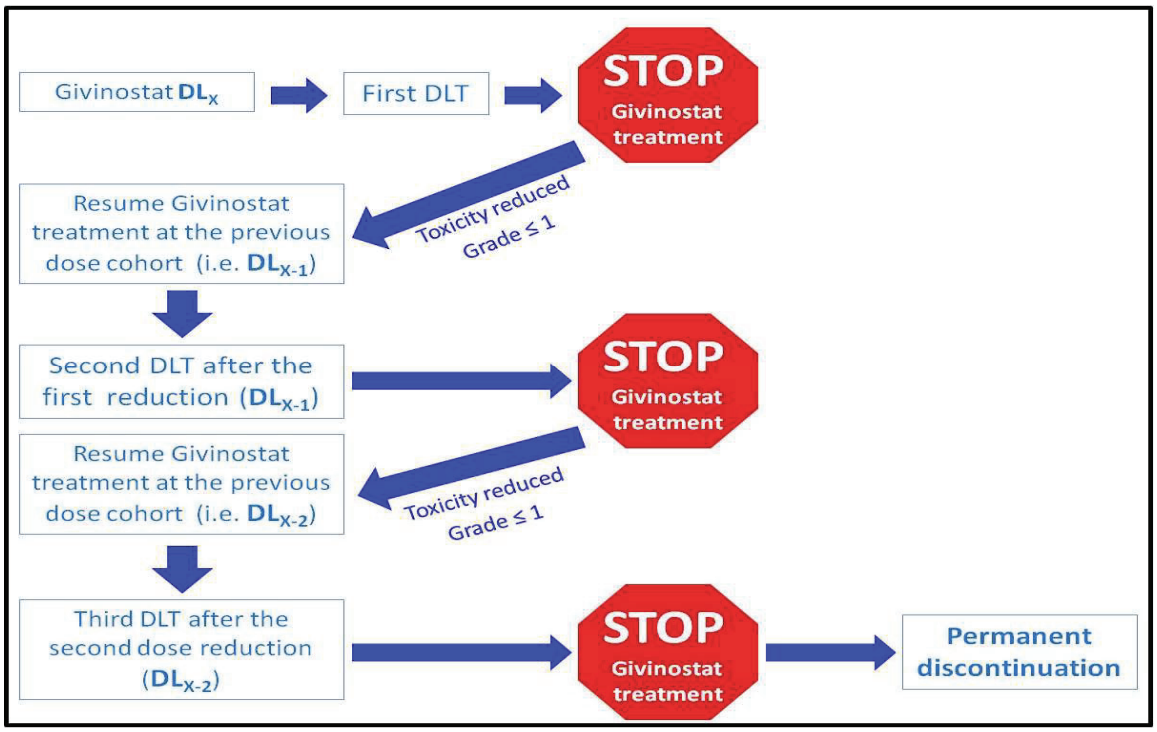
For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patients to continue the treatment with the study drug.

4.3.3.1 Dose modification criteria in *Part A*

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 (see paragraph 4.1.1.1 for the DLT definition). The first dose modification should be one dose level below the current dose, the second modification should be two dose levels below. Study drug may be resumed at lower dose level once the event resolves to at least grade 1 or baseline values. If toxicities meeting modification criteria occur after the second dose reduction, therapy must be discontinued. Figure 1 outlines the dose modifications scheme for all DLs of Givinostat monotherapy, with exception of DL0 (i.e. 50 b.i.d.) and DL1 (i.e. 100 mg b.i.d.) represented by Figures 2 and 3, respectively. Patients with unresolved toxicities **lasting 2 weeks or longer** will not be permitted to continue on study.

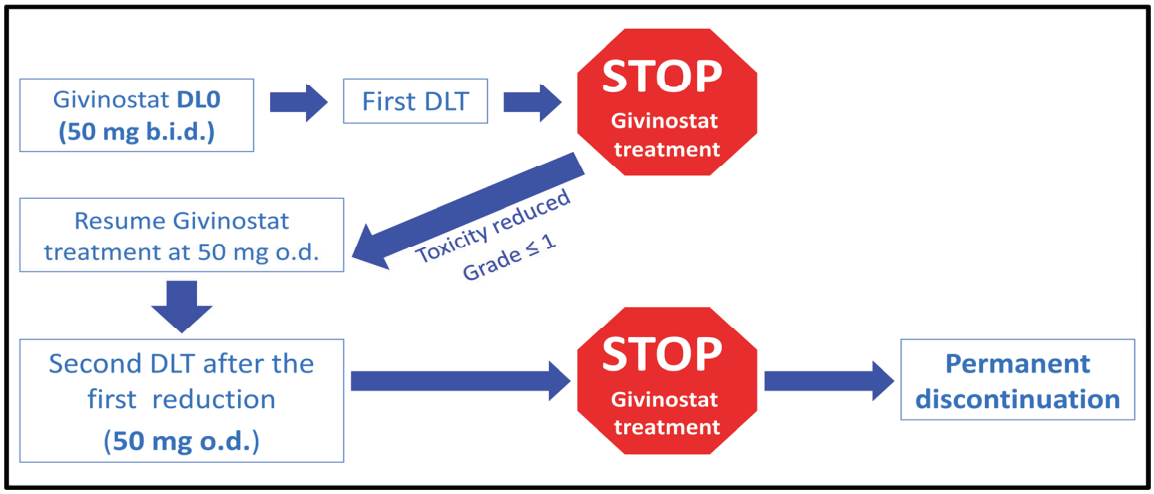
Patients experiencing Grade 3 or 4 unmanageable toxicity will require immediate dose interruption and notification to the Sponsor. Treatment for each new cycle will be delayed until dose limiting toxicities that are clearly not related to disease progression have resolved to at least Grade 1 or the patient's baseline.

Figure 1 - Criteria for dose modifications



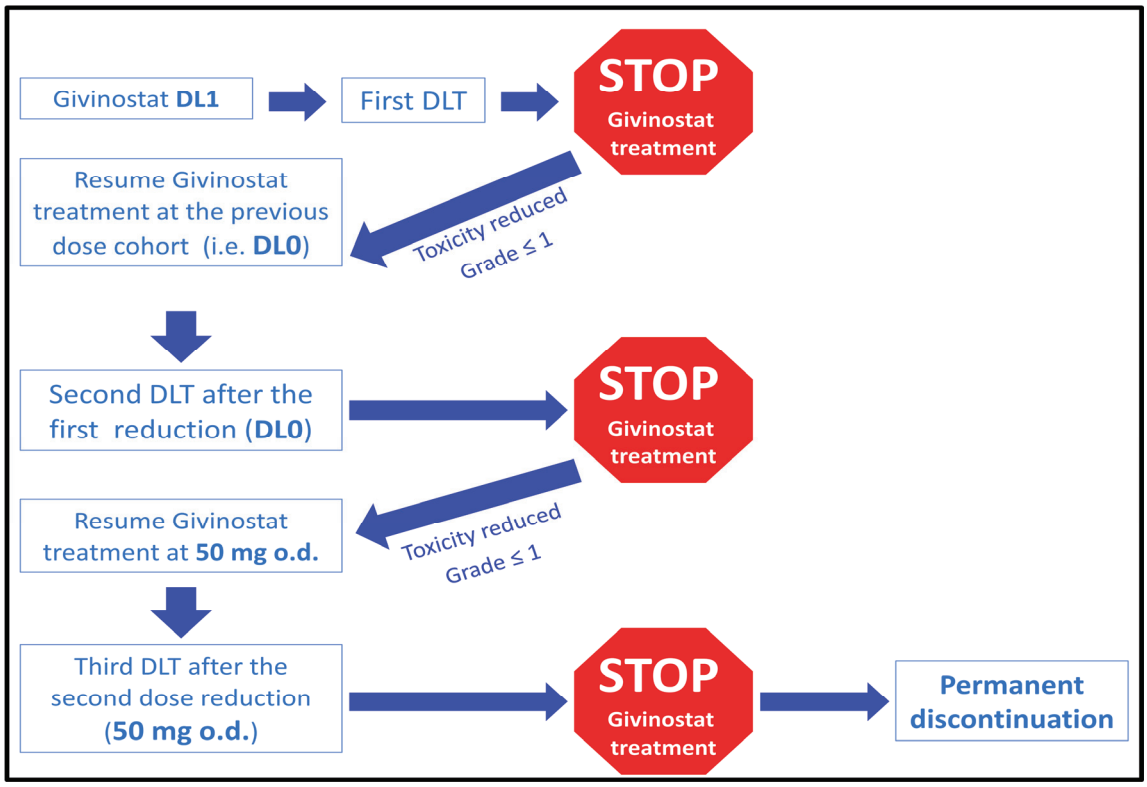
DLT is a Dose Limiting Toxicity. DL_x represents a Dose Level with the exception of DL0 (i.e. 50 mg b.i.d.) and DL1 (i.e. 100 mg b.i.d.), represented by Figures 2 and 3, respectively. DL_{x-1} represents the next lower Dose Level (first dose reduction). DL_{x-2} represents the next lower dose level after a first dose reduction (second dose reduction). Grade ≤ 1 represents the severity of AE.

Figure 2 - Criteria for dose modifications for patients treated in DL0



DLT is a Dose Limiting Toxicity. Grade ≤ 1 represents the severity of AE.

Figure 3 - Criteria for dose modifications for patients treated in DL1



DLT is a Dose Limiting Toxicity. Grade ≤ 1 represents the severity of AE.

4.3.3.2 Dose modification criteria in *Part B*

Dose adjustments are permitted for patients who do not tolerate the protocol-specified dosing schedule, in order to allow to these patients to continue the treatment with Givinostat. The guidelines described here below (i.e. see paragraph 3.3.3.2.1 and paragraph 3.3.3.2.2) need to be followed. The objective of the Givinostat dose adjustment rules described below 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 (see paragraph 3.3.3.2.1) 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 (see paragraph 3.3.3.2.2).

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).

Each dose modification has to be recorded on the CRF.

Of note, the dose modification criteria described in this paragraph (i.e. see paragraph 3.3.3.2.1 and paragraph 3.3.3.2.2 for details) will be followed also by patients initially dosed at lower dose levels in ***Part A*** that, after the definition of MTD, are allowed to escalate their Givinostat dose to the MTD for the remainder part of the study (***Part A***) at the discretion of the Investigator **and** after written authorization of Italfarmaco S.p.A..

4.3.3.2.1 Dose adjustments for safety reasons in *Part B*

In ***Part B***, the initial dose of Givinostat will be the MTD defined in ***Part A*** (i.e. 100 mg b.i.d.).

Based on evaluations performed as part of the visit procedures of the Day 28 of each Cycle up to the Cycle 5 (i.e. Cycle 1 Day 28, Cycle 2 Day 28, Cycle 3 Day 28, Cycle 4 Day 28, Cycle 5 Day 28) and/or in any necessary additional study visit, the Givinostat doses **have to be decreased** in case of the occurrence of at least one of the toxicities described in the Table 3.

The objective of these guidelines is to consider the patient's data, prior clinic-haematological response and dose tolerability, in order to achieve an optimized dose for each individual patient, or a balancing between the tolerable dose and the clinico-haematological response, that also take into account the natural course of the disease.

Reductions in Givinostat total daily dose for patients that meet dose reduction criteria (see Table 3 for details) will be achieved by adjusting the morning and evening administered dose level, since the total daily dose is equally divided between the morning and evening administration.

Table 3 - Dose reduction rules in *Part B*

Observed values/data	Action
Grade 1 thrombocytopenia (i.e. PLTs count < local LLN but ≥ 75 x 10^9/L)	***Total daily dose must be reduced of 50 mg/die***: • *For patients that are receiving the daily dose of 100 mg b.i.d., daily dose must be reduced to* ***75 mg b.i.d.***. • *For patients that are receiving a reduced daily dose of 75 mg b.i.d. or 50 mg b.i.d.,* ***daily dose must be evaluated*** based on the Investigator's decision **and** after discussion with the Sponsor's representative(s).
Grade 2 thrombocytopenia (i.e. PLTs count < 75 x 10^9/L but ≥ 50 x 10^9/L) ***or*** Grade 2 anemia (i.e. Hb value < 10 g/dL but ≥ 8 g/dL) ***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.	***Total daily dose must be reduced of 50 or 100 mg/die,*** *based on the Investigator's decision* ***and*** *after discussion with the Sponsor's representative(s)****:*** • *For patients that are receiving the daily dose of 100 mg b.i.d.*, daily dose should be reduced to ***75 mg b.i.d. or 50 mg b.i.d.***, based on the Investigator's decision **and** after discussion with the Sponsor's representative(s). • *For patients that are receiving a reduced daily dose of 75 mg b.i.d. or 50 mg b.i.d.,* ***daily dose must be evaluated*** based on the Investigator's decision **and** after discussion with the Sponsor's representative(s).
Grade 3 thrombocytopenia (i.e. PLTs count < 50 x 10^9/L but ≥ 25 x 10^9/L) ***or*** Grade 3 anemia (i.e. Hb value < 8 g/dL; transfusion indicated) ***or*** Grade 3 febrile neutropenia (i.e. ANC < 1.0 x 10^9/L with a single temperature of > 38.3°C / 101° F, or a sustained temperature ≥ 38°C / 100.4°F for more than one hour)	***Immediate temporary discontinuation of the treatment with Givinostat***. The treatment will be interrupted ***for at least one week***. ***Anyway***, the treatment for each new cycle will be delayed ***until the observed toxicity*** that is clearly not related to disease progression, ***has resolved to at least Grade 1 or the patient's baseline value***. Daily dose has to be restarted at ***75 mg b.i.d. or 50 mg b.i.d.***, based on the Investigator's decision **and** after discussion with the Sponsor's representative(s). Patients with unresolved toxicities **lasting 4 weeks or longer** will not be permitted to continue on study.

Table 3 - Dose reduction rules in *Part B* (*continue*)

Observed values/data	Action
Grade 4 thrombocytopenia (i.e. PLTs count ≤ 25 x 10^9/L) ***or*** Grade 4 anemia (i.e. life-threatening consequences; urgent intervention indicated) ***or*** Grade 4 febrile neutropenia (i.e. life-threatening consequences; urgent intervention indicated) ***or*** Grade ≥ 3 **unmanageable** toxicity	***Immediate temporary discontinuation of the treatment with Givinostat***. The treatment will be interrupted ***for at least one week***. ***Anyway***, the treatment for each new cycle will be delayed ***until the observed toxicity*** that is clearly not related to disease progression, ***has resolved to at least Grade 1 or the patient's baseline value***. ***The continuation of the study - and the study drug dosage - should be evaluated based on the Investigator's decision and Sponsor's recommendation***. Patients with unresolved toxicities **lasting 4 weeks or longer** will not be permitted to continue on study.

LLN is the Lower Limit of Normality of the value reported in each evaluation performed at local laboratory of each investigational site.

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).

Patients with unresolved toxicities **lasting 4 weeks or longer** will not be permitted to continue on study.

In order follow the evolution of the observed abnormalities up to its stabilization and/or normalization (i.e. event resolved to at least Grade 1 or baseline values) and also to provide sufficient data to make dose adjustment decisions, **it is strictly recommended** to perform additional study visits at least on bi-weekly basis upon occurrence of the following toxicities:

- Grade 1 thrombocytopenia (i.e. PLTs count < local LLN but ≥ 75 x 10^9/L);
- Grade 1 anemia (i.e. Hb value < local LLN but ≥ 10 g/dL),
- ANC < 2.0 x 10^9/L;
- Grade 2 non-haematological toxicities;
- Any SAE (*if feasible*).

In addition, additional study visits at least on weekly basis **should be performed** upon occurrence of the following toxicities:

- Grade ≥ 2 thrombocytopenia (i.e. PLTs count < 75 x 10^9/L);
- Grade ≥ 2 anemia (i.e. Hb value < 10 g/dL),
- ANC ≤ 1.5 x 10^9/L;
- **Drug-related** Grade ≥ 3 non-haematological toxicities;
- **Drug-related** SAE (*if feasible*).

Of note, the lowest dosage of Givinostat that can be dispensed to the patients in ***Part B*** is 50 mg b.i.d., i.e. a dosage that has been previously shown to be well tolerated. Of note, patients will self-administer daily Givinostat capsules at home at morning and at 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).

4.3.3.2.2 Dose increase for inadequate efficacy in *Part B*

In ***Part B***, the initial dose of Givinostat will be the MTD defined in ***Part A*** (i.e. 100 mg b.i.d.).

Based on evaluations performed as part of the visit procedures of the Day 28 of each Cycle up to the Cycle 5 (i.e. Cycle 1 Day 28, Cycle 2 Day 28, Cycle 3 Day 28, Cycle 4 Day 28, Cycle 5 Day 28) and/or in any necessary additional study visit, the Givinostat doses have to be decreased in case of the occurrence specific toxicities (see paragraph 4.3.3.2.1).

After a dose reduction, dosing may be restarted and then increased following recovery of the observed toxicity(ies) to controlled levels. The objective for restarting and then escalating after a reduction for safety reasons is to find the highest safe dose regimen of Givinostat for each patient that is necessary to obtain a clinico-haematological response, with increase in dose not more than the MTD defined in ***Part A*** (i.e. 100 mg b.i.d.).

After a dose reduction and in order to optimize the response for each individual patient avoiding specific drug-related toxicities, the Givinostat dosage **may be increased** for patients who meet all the following criteria, based on evaluations performed as part of the visit procedures of the Day 28 of each Cycle up to the Cycle 5 (i.e. Cycle 1 Day 28, Cycle 2 Day 28, Cycle 3 Day 28, Cycle 4 Day 28, Cycle 5 Day 28):

1. Inadequate efficacy as demonstrated by one or more of the following points:
   a) HCT ≥ 45%, ***or*** HCT < 45% but at least 1 phlebotomy performed after the first 3 weeks of treatment, ***or*** HCT < 45% but at least three point higher than the HCT obtained at baseline (i.e. HCT at baseline (in %) plus at least a value of 3%), ***or***
   b) WBCs count > 10 x 10^9/L, ***or***
   c) PLTs count > 400 x 10^9/L, **and**

2. PLTs count > local LLN, **and**
3. Hb value ≥ 12 g/dL, **and**
4. ANC ≥ 1.5 x 10^9/L.

Table 4 summarizes the dose increase rules to be apply for Givinostat dosage at the end (i.e. Day 28) of each Cycle of ***Part B*** up to Cycle 5 (i.e. Cycle 1 Day 28, Cycle 2 Day 28, Cycle 3 Day 28, Cycle 4 Day 28, Cycle 5 Day 28). The objective of these guidelines is to consider the patient's data, prior clinico-haematological response and dose tolerability, in order to achieve an optimized dose for each individual patient, or a balancing between the tolerable dose and the clinico-haematological response, that also take into account the natural course of the disease.

Table 4 - Dose increase for inadequate efficacy in *Part B*

Observed values/data	Action
1. Inadequate efficacy as demonstrated by one or more of the following points: a) HCT ≥ 45%, ***or*** HCT < 45% but at least 1 phlebotomy performed after the first 3 weeks of treatment, ***or*** HCT < 45% but at least three point higher than the HCT obtained at baseline (i.e. HCT at baseline (in %) plus at least a value of 3%), **or** b) WBCs count > 10 x 10^9/L, **or** c) PLTs count > 400 x 10^9/L, **and** 2. PLTs count > local LLN, **and** 3. Hb value ≥ 12 g/dL, **and** 4. ANC ≥ 1.5 x 10^9/L.	***Total daily dose may be increased of 50 mg/die:*** • *For patients that are receiving a reduced daily dose of 75 mg b.i.d.,* daily dose must be increased to ***100 mg b.i.d.***. • *For patients that are receiving a reduced daily dose of 50 mg b.i.d.,* daily dose must be increased to ***75 mg b.i.d.***. • ***Only for patients of Part A*** *that are receiving a reduced daily dose of 50 mg o.d.,* daily dose must be increased to ***50 mg b.i.d.***.

The total daily dose increase may be no greater than an increase of 50 mg/die, since the following dose increase rules will apply as detailed in the Table 4:

- *For patients that are receiving a reduced daily dose of 75 mg b.i.d.*, the dose increase criteria allow to receive a maximum dosage of 100 mg b.i.d.;
- *For patients that are receiving a reduced daily dose of 50 mg b.i.d.*, the dose increase criteria allow to receive a maximum dosage of 75 mg b.i.d..

- *Only for patients of* ***Part A*** *that are receiving a reduced daily dose of 50 mg o.d.*, the dose increase criteria allow to receive a maximum dosage of 50 mg b.i.d..

Therefore, total daily dose may never exceed the MTD defined in ***Part A*** (i.e. 100 mg b.i.d.).

4.3.3.3 Treatment interruption and treatment discontinuation in *Parts A* and *B*

In some circumstances, it may be necessary to temporarily interrupt treatment as a result of adverse experiences that may have an unclear relationship to study drug. Study drug may be withheld by the Investigator at any time if there is concern about patient safety and for all aspects of the conduct of the protocol, since the safety of the individual patient is paramount. Treating Investigator may employ any means necessary to ensure patient safety, particularly in medical circumstances not anticipated by this protocol.

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

If the patient inadvertently misses a drug dose, no additional trial medication should be taken that day or in the next days in the effort to replace the material that has been missed.

If vomiting occurs, no additional trial medication should be taken that day in an effort to replace the material that has been vomited.

If the study drug is interrupted for any reason for more than 4 weeks continuously, dosing may be not be restarted.

Patients have the right to withdraw from the study at any time for any reason. The Investigator has the right to withdraw patients from the study due to medical reasons according to his/her discretion.

When patients discontinue study medication, the reason must be categorized in the case report form (CRF) as one of the following:

1. study completed;
2. adverse event(s);
3. disease progression;
4. protocol violation;
5. patient withdrew Informed Consent Form;
6. lost at follow-up (despite every effort made to contact the patient);

7. physician decision due to safety reasons;
8. sponsor decision (see paragraph 8.7);
9. lack of compliance;
10. patient found not eligible;
11. death;
12. pregnancy.

If a pregnancy occurs, the patient will be replaced and another patient in that DL should be recruited.

If the patient discontinues the study because of an adverse event whether or not drug related, he/she must be followed until resolution or stabilization of the event, whichever occurs first.

In case of lack of compliance or in case the patient is found not eligible, the patient discontinuation have to be discussed between Investigator and Sponsor.

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

If the patient needs to take one of the concomitant medications included in list of "Drugs with risk of Torsades de Pointes" (see Appendix C) the treatment with Givinostat is to be promptly discontinued and the patient must leave the study.

In case of multiple reasons (e.g. patient withdraws the consent for toxicity), "adverse events" should be indicated as the primary reason whenever applicable. All relevant information related to the reason for treatment discontinuation including contributory factors must be included on the 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. Should any drug-related AE still be ongoing beyond the last scheduled visit, this must be followed at subsequent follow-up visits until recovery. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance every effort should 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 must be included on the CRF.

4.4 Treatments

4.4.1 Investigational Medicinal Product (IMP)

Completed and updated data following described are reported in the Section 4 "Physical, chemical and pharmaceutical properties and formulation" of the current Investigator Brochure Dossier related to ITF2357.

Givinostat is a histone-deacetylases inhibitor.

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 Italfarmaco S.p.A. research code). Therefore, the dosages/concentrations of the study drug are expressed as Givinostat hydrochloride monohydrate.

The product will be supplied 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.

4.4.1.1 Dosage and administration

In ***Part A*** patients will 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, additionally DLs may be used to establish the MTD (for more details, see paragraph 4.1.1.3).

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

Dose adjustments are permitted for patients who do not tolerate the protocol-specified dosing schedule, in order to allow to these patients to continue the treatment with Givinostat (see paragraph 4.3.3.1 and paragraph 4.3.3.2). 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 will self-administer daily Givinostat capsules at home as instructed by the Investigator (see paragraph 4.4.7.2 and paragraph 4.4.7.4), except for the first drug administration (i.e. Day 1 of the Cycle 1). Patients will not 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). Study drug will be 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 will 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 at 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 dosage (i.e. 50 mg b.i.d, or 100 mg b.i.d., or 150 mg/die), patients will self-administer daily Givinostat capsules at home at morning and at 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 can be dispensed to the patients is 100 mg b.i.d.. In all the possible dosage (i.e. 50 mg b.i.d., 75 mg b.i.d., 100 mg b.i.d.), patients will self-administer daily Givinostat capsules at home at morning and at 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 protocol-specified dosing schedule, in order to allow to these patients to continue the treatment with Givinostat. The guidelines described here above (i.e. see paragraph 4.3.3.2.1 and paragraph 4.3.3.2.2) 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 will be mandated for specific toxicities (see paragraph 4.3.3.2.1) and dose increases after an initial dose reduction will be allowed in the case of inadequate efficacy at the reduced dosage.

Each dose modification has to be recorded on the CRF.

4.4.2 Treatment assignment

No randomization procedures are required in this study.

In ***Part A***, patients will be assigned to the DL0 (i.e. 50 mg b.i.d.) when no treatment slots in higher dose levels are available.

4.4.3 Patient numbering and screening

Each patient will be identified in the study by a patient code.

During the screening period (i.e. after the informed consent form signature and before the recruitment confirmation by the Italfarmaco S.p.A. or its designee), the patient code will be named **patient screening ID** and will be a combination of his/her site ID, study part ID and patient screening number.

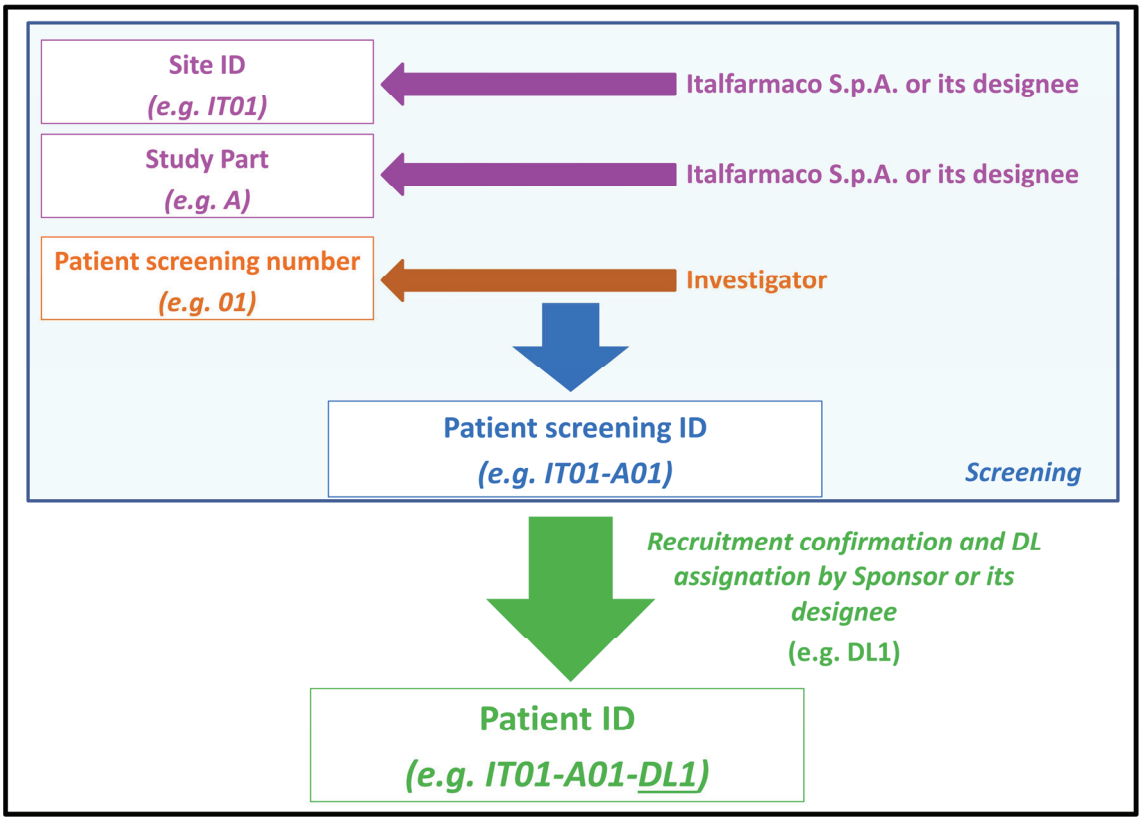
Both the site ID and the study part ID (i.e. "A" or "B" for ***Part A*** or ***Part B***, respectively) will be assigned by the Sponsor or its designee to the investigator site.

Upon signing the informed consent form, the patient screening number will be assigned by the Investigator. At each site, the first patient will be assigned patient number "01", and subsequent patients will be assigned consecutive numbers (e.g. the second patient will be assigned patient number "02", the third patient will be assigned patient number "03", etc. etc.).

When a study site has a patient ready to enrol, prior to dosing the site will compile a request for registration Form and send it to Italfarmaco S.p.A. or its designee in order to obtain the patient ID. The request for registration contains the site ID, the study part ID, the assigned patient screening number, a checklist related to the inclusion/exclusion criteria to verify the eligibility of the patient and collect some other information (e.g. date of birth, date of informed consent obtained). If the patient is eligible, Italfarmaco S.p.A. or its designee will confirm the enrolment of the patient assigning the related dose level and the **patient ID** (i.e. the patient code after the enrolment confirmation) which will be a combination of patient screening ID and dose level ID.

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

The following scheme will resume the patient identification process:



If the patient will fail to be enrolled for any reason, the reason will be entered in the study CRF within 2 days that the patient is not enrolled.

According to ICH-GCP guidelines, the Investigator will maintain a patient identification list, which ensures a distinctive identification of the patients by their name to screening numbers, date of birth, sex and date of inclusion.

4.4.4 Blinding

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

4.4.5 Concomitant therapy

Patients must **NOT** receive the following treatments during the study:

a) Other investigational drugs while on this study;
b) Cytotoxic agents, interferons or other approved treatment for cMPN other than aspirin/cardio-aspirin;
c) Any drug known to provoke TdP (see Appendix C).

Other concomitant medications (e.g. symptomatic treatment of pruritus) and significant non-drug therapy (e.g. phlebotomy, blood transfusion) are permitted and must be recorded in the CRF.

4.4.6 Treatment compliance

The Investigator will record in the CRF the assigned dose of Givinostat and any dose reduction (*if applicable*) to allow the evaluation of compliance to treatment.

At each visit, patients will bring back to the study site all drug bottles previously received (i.e. used, partially used and unused) and receive a new supply. The number of residual capsules in the dispensed bottles will be counted by the Investigator and reported in the CRF.

Then the bottles used, partially used and unused will be collected and sent back to Italfarmaco S.p.A. or their designee periodically or at the end of the study.

Compliance with Givinostat treatment will be calculated by Italfarmaco S.p.A. or its designee based on the 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.

4.4.7 Drug supply

4.4.7.1 Packaging

The packaging will consist 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.

Depending on the need of supply of each Centre (e.g. number of treated patients) a variable number of bottles will be packed in a carton box for shipping.

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

4.4.7.2 Labelling

The IMP will be appropriately labelled at Italfarmaco S.p.A. or their designee (e.g. external providers when requested by the local law, CMO).

Label of the bottles will comply with the legal requirements of each country and will be printed in the local language.

The labels will show all the information requested according to the Annex 13 to the Good Manufacturing Practice (published by the Commission in The rules governing medicinal products in the European Community, Volume 4) and the local drug law (*if any*) and the local regulatory requirements. Only the patient specific bottle will be labelled with a tear-off label.

The label of the medicinal product includes in the local language at least the following data:

- Sponsor's study code;
- EudraCT No.;
- Patient ID;
- Name, address and telephone number of the Sponsor or/and the CRO or their delegates (*if applicable*);
- Name of the Investigator;
- Name and strength of the medicinal product;
- Pharmaceutical dosage form;
- Route of administration;
- Quantity of dosage units;
- Visit in which the patient receive the study drug;
- Directions for use (reference may be made to a leaflet or other explanatory document intended for the trial patient or person administering the product);
- Batch number;
- Expiry date;
- Declaration of the intended purpose (e.g. for clinical trial use only);
- Storage conditions;
- The wording "Keep out of reach of children".

The patient ID and the visit in which the patient receive the study drug will be reported on every label by the Investigator.

The Investigator will also provide the patient with written instructions on the number of capsules to be taken at each administration (i.e. dosage schedule).

4.4.7.3 Storage

The IMP will be appropriately stored at Italfarmaco S.p.A. or their designee (e.g. external providers when requested by the local law, CMO) until distribution to the investigational sites.

The investigational site will store the IMP under the same conditions, as specified in the label, ensuring that it is not accessible to unauthorized persons till its dispensing to patients.

Detailed instructions for the IMP storage and management will be provided in a separate and specific IMP handling instruction manual.

4.4.7.4 IMP dispensing

All IMP supplies are to be used only for this protocol and not for any other purpose.

Investigator will be responsible for the delivery of IMP to the patient according to the protocol and to instruct the patient to take the IMP as per protocol.

Patients will be administered the IMP on an outpatient basis.

At each visit, the Investigator will supply the patients with the appropriate number of bottles sufficient to cover the period between two visits.

The Investigator will also provide the patient with written instructions on the number of capsules to be taken at each administration.

4.4.7.5 IMP accountability

The Investigator will maintain accurate records of the disposition of all IMP received, distributed to patients (including date and time) and accidentally destroyed. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. **At each visit**, patients will bring back to the study site **all** drug bottles previously received (**used, partially used and unused**) and receive a new IMP supply.

At the study close-out, and, as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and the completed drug forms to Italfarmaco S.p.A., Dipartimento di Tecnica Farmaceutica, Viale Fulvio Testi, 330, 20126 Milan (MI), Italy or its designee (e.g. CMO).

Only in some particular cases, after the authorization of Italfarmaco S.p.A. (or after a signed agreement between the investigational site and Italfarmaco S.p.A.), these materials can be destroyed locally.

4.5 Study Procedures

Patient must be followed at the study centre according to the visit schedule and assessments outlined in the flow-chart (Appendix A).

Patient's consent must be obtained prior to any study-specific procedures.

Prior to start any study procedure, patients will be informed in details by the Investigator about the nature of the study, its purpose and procedures and about the possible risks and benefits resulting from study participation. Each patient will be given written information and the opportunity to ask questions. Patients who have voluntarily signed the written informed consent may start the following study procedures.

4.5.1 Laboratory evaluations and vital signs assessment

The laboratory examinations (haematology, blood chemistry and urinalysis) will be performed in the local laboratory of each site. In addition, the vital signs assessment, the ECG assessment/evaluation and the QTc determination (according with Bazett's correction formula, Appendix D) will be performed at each investigational site.

All these results will be transcribed into the CRF and the original signed and dated laboratory print-out/tracings, including the ECG and source document, will be monitored and stored at the study site. Of note, if the first ECG evaluation demonstrates 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) must be performed. The averaged value of these three ECG evaluations has to be used for the evaluation of the QTc interval of the related visit. In the CRF all the performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*.

The laboratory examinations, the vital signs assessment, the ECG evaluation including the QTc determination are listed below:

1) **Haematology**

   Red blood cells (RBC) count, haematocrit (HCT), haemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), white blood cells (WBC) count (full and differential), platelets (PLT) count.

2) **Blood chemistry**

   ALT/SGPT, AST/SGOT, alkaline phosphatase (ALP), total bilirubin, lactic dehydrogenase (LDH), creatinine, blood urea nitrogen (BUN) or Urea (see Appendix F to convert Urea to BUN), glucose, sodium (Na), potassium (K), calcium (Ca), chloride (Cl), magnesium (Mg), albumin, eGFR determination (according with the Mayo Clinic Quadratic Equation).

3) **Urinalysis**

   pH, specific gravity, protein, glucose.

4) **Vital signs**

   Respiratory rate, pulse rate and sitting blood pressure will be measured after 5 minutes of rest.

5) **ECG and QTc**

   ECG assessment and evaluation, QTc determination (according with Bazett's correction formula, Appendix D). Of note, if the first ECG evaluation demonstrates 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) must be performed. The averaged value of these three ECG evaluations has to be used for the evaluation of the QTc interval of the related visit. In the CRF all the performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*.

4.5.2 Physical examination

Information about the physical examination must be present in the source documentation at the study site. Significant findings that are present prior to the start of study drug must be included in the Medical History section of the CRF or Current Medical Conditions section of the CRF. Significant findings reported after the start of treatment with the study drug that meet the definition of an AE must be recorded in the Adverse Event section of the CRF.

Study visit schedule and required evaluations and procedures to be performed at each study visit are described below and summarized in the flow-chart in Appendix A. Methods of assessment of safety and efficacy are described in the paragraph 4.6 and paragraph 4.7 of the present protocol.

4.5.3 Spleen evaluation, PK and PD characterization, molecular examinations and bone marrow histological evaluation

4.5.3.1 Spleen evaluation

The spleen evaluation must be performed at the study centre according to the visit schedule outlined in the flow-chart (Appendix A).

The spleen evaluation will be performed during the study 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) should be used on a patient throughout the study, *if possible*.

If possible, the spleen dimension will be evaluated as longitudinal diameter (hereafter "A"), antero-posterior diameter (hereafter "B"), transversal diameter (hereafter "C") and Splenic Volumetric Index (hereafter "SVI"):

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

No spleen evaluation will be performed in splenectomised patients.

4.5.3.2 PK characterization

Approximately 5.0 mL of blood for pharmacokinetic assessment will be collected as following described:

1) Day 1 of Cycle 1 of ***Parts A*** and ***B***: before the first Givinostat dose (pre-dose) and 2, 3 and 8 (before the second Givinostat dose) hours after the first drug administration (Appendix A).

   e.g.: the PK pre-dose evaluation will be performed at 7.45 a.m. of Day 1 (pre-dose) of Cycle 1 of ***Parts A*** and ***B*** and after that the patient will take the first drug

administration (e.g. at 8.00 a.m.); then, the patient will perform the PK post-dose evaluations at 10.00 a.m. (hour 2), 11.00 a.m. (hour 3) and at 16.00 p.m. (hour 8).

2) Day 28 of the Cycle 1 of ***Part A***: before the first daily Givinostat dose (pre-dose) and 1, 2, 4 and 8 (before the second Givinostat dose) after the first daily drug administration (Appendix A).

   e.g.: the PK pre-dose evaluation will be performed at 7.45 a.m. of Day 28 of Cycle 1 (pre-dose) of ***Part A*** and after that the patient will take the first daily drug administration (e.g. at 8.00 a.m.); then, the patient will perform the PK post-dose evaluations at 9.00 a.m. (hour 1), 10.00 a.m. (hour 2), 12.00 p.m. (hour 4) and at 16.00 p.m. (hour 8).

3) Day 28 of the Cycles 2, 3, 4, 5, and 6 of ***Part A***: before the first daily Givinostat dose (pre-dose) (Appendix A).

   e.g.: the PK pre-dose evaluation will be performed at 7.45 a.m. of Day 28 of Cycle 2 and beyond Cycles (i.e. Cycles 3, 4, 5 and 6) of ***Part A*** (pre-dose) and after that the patient will take the first daily drug administration (e.g. at 8.00 a.m.).

4) Day 28 of Cycle 2 of ***Part B***: before the first daily Givinostat dose (pre-dose) and 1, 2, 4 and 8 (before the second Givinostat dose) hours after the first daily drug administration (Appendix A).

   e.g.: the PK pre-dose evaluation will be performed at 7.45 a.m. of Day 28 of Cycle 2 (pre-dose) of ***Part B*** and after that the patient will take the first daily drug administration (e.g. at 8.00 a.m.); then, the patient will perform the PK post-dose evaluations at 9.00 a.m. (hour 1), 10.00 a.m. (hour 2), 12.00 a.m. (hour 4) and at 16.00 p.m. (hour 8).

The PK samples should be drawn as closely to the predefined time as possible.

The exact timing of PK sampling could be adjusted based on emerging clinical and preclinical data.

For all time points an additional PK blood sample will be collected as back-up sample.

This assessment is mandatory and will be performed by a central laboratory. The exact date and time of the PK blood draws will be recorded along with the date and time of the last dose of study drug preceding the blood draw. Additional information about the PK time points, instructions for sample preparation and shipment will be provided in the related study handling manual.

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.

4.5.3.3 PD characterization

Approximately 4.0 mL of blood for pharmacodynamic markers will be collected before the first Givinostat dose (pre-dose) and 12 hours after the first Givinostat dose (post-dose) at Day 1 of Cycle 1 both in ***Part A*** and in ***Part B*** for measurement of levels of

molecular markers, to evaluate the pharmacodynamic effect of Givinostat and to identify markers predictive of clinical benefit of Givinostat (Appendix A). In addition, pharmacodynamic evaluations will be performed also using an aliquot of the PK samples collected at time points described in the paragraph 4.5.3.2 [**34**]. 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 pharmacodynamic 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 will be collected as back-up sample.

This assessment is mandatory and will be performed by a central laboratory. The exact date and time of the PD blood draws will be recorded along with the date and time of the last dose of study drug preceding the blood draw. Instructions for sample preparation and shipment will be provided in a separate and specific laboratory manual.

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.

4.5.3.4 $JAK2^{V617F}$ characterization

$JAK2^{V617F}$ characterization (i.e. $JAK2^{V617F}$ allele burden evaluated by quantitative RT-PCR) will be performed in a central laboratory (Appendix E). Detailed instructions for sample preparation and shipment will be provided in a separate and specific laboratory manual.

For all time points a blood sample will be collected as back-up sample.

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.

4.5.3.5 Molecular examinations

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

Detailed instructions for sample preparation and shipment will be provided in a separate and specific laboratory manual.

The results will be transcribed into the CRF by the central laboratory team or its designee and the original signed and dated laboratory print-out/tracings will be 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.

4.5.3.6 Bone marrow histological evaluation

A bone marrow histological evaluation will be performed to all patients recruited 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) [**33**] (see paragraph 4.8.7).

This examination will be performed in the local laboratory of each site. The results of this test will be transcribed into the 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, will be monitored and stored at the study site.

Please note that, in case the patient performs the bone marrow histological evaluation as requested by the "**new**" ELN criteria (i.e. the **revised** ELN response criteria) [**33**] (see paragraph 4.8.7) – 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 Informed Consent Form), 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 will be transcribed into the 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, will be monitored and stored at the study site.

In case the patient drops-out the study during the first 3 Cycles (i.e. before the Day 28 of Cycle 3), this evaluation has not to be performed at End of Study visit.

Finally, in case the patient refuses to provide this written consent to perform the bone marrow evaluation, this patient can be anyway 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 [**33**], and the evaluation of the effect of Givinostat on each single response parameter according to the **revised** ELN response criteria [**33**]).

4.5.4 Visit schedule

Patient must be followed at the study centre according to the visit schedule and assessments outlined in the flow-chart (Appendix A).

The investigative team at the study site will be responsible for all treatment administrations and evaluations throughout the study period.

4.5.4.1 *Part A*

4.5.4.1.1 Pre-treatment evaluations (up to 4 weeks: -28 to Day -1)

The following procedures will be performed at the pre-treatment visit of Cycle 1 of ***Part A*** as reported below:

- Informed consent signing;
- Demographic data (race, sex and date of birth);
- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
- Medical history;
- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), height, weight, body temperature and ECOG performance status;
- Pregnancy test (*if indicated*);
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN or Urea (as per site-specific clinical practice; see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin, eGFR determination (according with the Mayo Clinic Quadratic Equation);
- ECG, QTc determination (according with Bazett's correction formula);
- Urinalysis: pH, specific gravity, protein, glucose;
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- Spleen evaluation by MRI or CT scan;
- Collection of a blood sample for the quantitative RT-PCR evaluation of $JAK2^{V617F}$ mutational status on peripheral blood (PB) granulocyte;
- Assessment of disease-related symptoms using the MPN-SAF QOL Questionnaire;
- Request of enrolment and receipt of patient ID.

Appendix A (in particular, paragraph 10.1.1.1) summarize timing information.

Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status [28] ≤ 1 within 7 days of initiating study drug.

The pregnancy test (*if indicated*) has to be 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 must be confirmed with a serum pregnancy test and the result recorded in the CRF.If the first ECG evaluation demonstrates 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) must be performed. The averaged value of these three ECG evaluations has to be used for the evaluation of the QTc interval requested by the exclusion criterion n. 3. In the CRF all the performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*.

Patients with splenomegaly will perform the spleen evaluation as per site-specific clinical practice. Therefore, patients with splenomegaly before the treatment start will be followed according to institutional guidelines (i.e. MRI or CT scan). The same imaging technique and the same instrument should be used on a patient throughout the study, *if possible*. No spleen evaluation will be performed in splenectomised patients.

Pre-treatment evaluations will be performed at one or more clinic visit to determine eligibility for the study. Pre-treatment evaluations must be performed up to 4 weeks before the treatment start within **± 7 days**.

If all eligibility criteria are met at the pre-treatment visit, the treatment with Givinostat can start.

After the check that all eligibility criteria are met by the patient and in any case before the treatment start, **all patients with an uncontrolled HCT (i.e. HCT ≥ 45%) have to perform at least one phlebotomy to normalize (*if possible*) the HCT value (i.e. HCT <45%).**

In case of patients phlebotomy-dependent, all efforts have to be afforded by Investigators to record all phlebotomies witch recruited patients experienced at least 6 months before the treatment start.

4.5.4.1.2 Cycle 1

Appendix A (in particular, paragraph 10.1.1.1) summarize timing information.

Patients can take drug at home, except for the first drug administration.

If the first ECG evaluation demonstrates 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) must be performed. The averaged value of these three ECG evaluations has to be used for the evaluation of the QTc interval. In the CRF all the performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*.

Day 1

The following procedures must be performed exactly at Day 1 of Cycle 1 of ***Part A*** as reported below:

1) **Pre-dose evaluations:**

   The following procedures will be performed **before the first Givinostat dose** as reported below:

   - Adverse event recording;
   - Concomitant medications (drugs);
   - Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
   - Physical examination, weight, body temperature and ECOG performance status;
   - Vital signs (blood pressure, pulse rate, respiratory rate);
   - Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN or Urea (as per site-specific clinical practice; see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin, eGFR determination (according with the Mayo Clinic Quadratic Equation);
   - ECG, QTc determination (according with Bazett's correction formula);
   - PD sample collection;
   - PK sample collection and preparation, in order to allow to perform both the PK and PD evaluations starting from the same sample [**34**].

2) **Post-dose evaluations:**

   The following procedures will be performed **after the first Givinostat dose** as reported below:

   - Adverse event recording;
   - Concomitant medications (drugs);
   - Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
   - Vital signs (blood pressure, pulse rate, respiratory rate) ***4 hours after the first Givinostat dose***;
   - ECG, QTc determination (according with Bazett's correction formula) ***3 hours after the first Givinostat dose***;
   - PD sample collection ***12 hours after the first Givinostat dose***;

- PK sample collection (2, 3 and 8 hours post-dose) and preparation, in order to allow to perform both the PK and PD evaluations starting from the same sample [**34**];
- First Givinostat dose and accountability.

Day 2

The following procedures will be performed exactly at Day 2 of Cycle 1 of ***Part A*** as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status;
- ECG, QTc determination (according with Bazett's correction formula);
- Used/unused/partially used Givinostat supply return, Givinostat administration and Givinostat accountability.

Days 3 and 4

The following procedures will be performed exactly at Days 3 and 4 of Cycle 1 of ***Part A*** as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
- Used/unused/partially used Givinostat supply return, Givinostat administration and Givinostat accountability.

Days 8, 15 and 22

The following procedures will be performed at Days 8, 15 and 22 of Cycle 1 of ***Part A*** (within **± 3 days)** as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);

- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status;
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN or Urea (as per site-specific clinical practice; see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin, eGFR determination (according with the Mayo Clinic Quadratic Equation);
- ECG, QTc determination (according with Bazett's correction formula);
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- Used/unused/partially used Givinostat supply return, Givinostat administration and Givinostat accountability.

Day 10

The following procedures will be performed at Day 10 of Cycle 1 of ***Part A*** (within **± 3 days**) as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
- Used/unused/partially used Givinostat supply return, Givinostat administration and Givinostat accountability.

Days 28

The following procedures will be performed at Day 28 of Cycle 1 of ***Part A*** (within **± 3 days)** as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status;
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN or Urea (as per site-specific clinical practice; see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin, eGFR determination (according with the Mayo Clinic Quadratic Equation);
- ECG, QTc determination (according with Bazett's correction formula);

- Urinalysis: pH, specific gravity, protein, glucose;
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- PK sample collection (pre-dose and 1, 2, 4 and 8 hours post-dose) and preparation, in order to allow to perform both the PK and PD evaluations starting from the same sample [**34**];
- Used/unused/partially used Givinostat supply return, Givinostat administration and Givinostat accountability.

End of Study

In case of the patient drops-out of the study, the following procedures will be performed **7 days after last drug intake** (within **± 3 days**) as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status;
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN or Urea (as per site-specific clinical practice; see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin, eGFR determination (according with the Mayo Clinic Quadratic Equation);
- ECG, QTc determination (according with Bazett's correction formula);
- Urinalysis: pH, specific gravity, protein, glucose;
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- Spleen evaluation by MRI or CT scan;
- Therapeutic response evaluation according to the clinico-haematological ELN response criteria [**21**] (see paragraph 4.6.1);
- Assessment of disease-related symptoms using the MPN-SAF QOL Questionnaire;
- Used/unused/partially used Givinostat supply return and Givinostat accountability.

As reported also in the paragraph 4.3.3, if the patient discontinues for any reason (including discontinuation for pregnancy), with drug related adverse event ongoing at study end, he/she must be followed until resolution or stabilization of the event or until it is reasonable to consider the event not drug related any more or until the start of a new treatment, whichever occurs first.

If the patient needs to take one of the concomitant medications included in list of "Drugs with risk of Torsades de Pointes" (see Appendix C) the treatment with Givinostat is to be promptly discontinued and the patient must leave the study.

In case of multiple reasons (e.g. patient withdraws the consent for toxicity), "adverse events" should be indicated as the primary reason whenever applicable. All relevant information related to the reason for treatment discontinuation including contributory factors must be included on the 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. Should any drug-related AE still be ongoing beyond the last scheduled visit, this must be followed at subsequent follow-up visits until recovery. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance every effort should 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 must be included on the CRF.

At study close-out, and as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and the completed drug forms to Italfarmaco S.p.A., Dipartimento di Tecnica Farmaceutica, Viale Fulvio Testi, 330, 20126 Milan (MI), Italy, or their designee.

Only in some particular cases, after the authorization of Italfarmaco S.p.A. (or after a signed agreement between the investigational site and Italfarmaco S.p.A.), these materials can be destroyed locally.

4.5.4.1.3 Cycles 2, 3, 4, 5 and 6

Appendix A (in particular, paragraph 10.1.1.2) summarize timing information.

Patients with splenomegaly will perform the spleen evaluation as per site-specific clinical practice. Therefore, patients with splenomegaly before the treatment start will be followed according to institutional guidelines (i.e. MRI or CT scan). The same imaging technique and the same instrument should be used on a patient throughout the study, if possible. No spleen evaluation will be performed in splenectomised patients. The spleen evaluation must be performed at the study centre according to the visit schedule outlined in the flow-chart (Appendix A).

If the first ECG evaluation demonstrates 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) must be performed. The averaged value of these three ECG

evaluations has to be used for the evaluation of the QTc interval. In the CRF all the performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*.

Day 1

The following procedures will be performed at Day 1 of Cycles 2, 3, 4, 5 and 6 of ***Part A*** (within **± 3 days**) as reported below:

- First Givinostat dose of the related cycle and accountability.

Day 28 of Cycles 2, 4 and 5

The following procedures will be performed at Day 28 of Cycles 2, 4 and 5 of ***Part A*** (within **± 3 days**) as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status;
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN or Urea (as per site-specific clinical practice; see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin, eGFR determination (according with the Mayo Clinic Quadratic Equation);
- ECG, QTc determination (according with Bazett's correction formula);
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- PK sample collection (pre-dose) and preparation, in order to allow to perform both the PK and PD evaluations starting from the same sample [**34**];
- Used/unused/partially used Givinostat supply return, Givinostat administration and Givinostat accountability.

Day 28 of Cycles 3 and 6

The following procedures will be performed at Day 28 of Cycles 3 and 6 of ***Part A*** (within **± 3 days**) as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);

- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status;
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN or Urea (as per site-specific clinical practice; see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin, eGFR determination (according with the Mayo Clinic Quadratic Equation);
- ECG, QTc determination (according with Bazett's correction formula);
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- PK sample collection (pre-dose) and preparation, in order to allow to perform both the PK and PD evaluations starting from the same sample [**34**];
- Spleen evaluation by MRI or CT scan;
- Therapeutic response evaluation according to the clinico-haematological ELN response criteria [**21**] (see paragraph 4.6.1);
- Collection of a blood sample for the quantitative RT-PCR evaluation of $JAK2^{V617F}$ mutational status on peripheral blood (PB) granulocyte;
- Assessment of disease-related symptoms using the MPN-SAF QOL Questionnaire;
- Givinostat administration (only for ***cycle 3***);
- Used/unused/partially used Givinostat supply return and Givinostat accountability.

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 [**21**] (see paragraph 4.6.1);.

End of Study

The following procedures will be performed **at the end of study visit** (in case of completed study) **or 7 days after last drug intake** (in case of the patient drops-out of the study) **(within** ± 3 days**)** as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);

- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status;
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN or Urea (as per site-specific clinical practice; see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin, eGFR determination (according with the Mayo Clinic Quadratic Equation);
- ECG, QTc determination (according with Bazett's correction formula);
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- Spleen evaluation by MRI or CT scan;
- Therapeutic response evaluation according to the clinico-haematological ELN response criteria [**21**] (see paragraph 4.6.1);
- Collection of a blood sample for the quantitative RT-PCR evaluation of $JAK2^{V617F}$ mutational status on peripheral blood (PB) granulocyte;
- Assessment of disease-related symptoms using the MPN-SAF QOL Questionnaire;
- Used/unused/partially used Givinostat supply return and accountability.

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 the Cycle 6 Day 28 visit can be counted for the End of Study visit.

In addition, in case the patient completes the study (i.e. performs all the evaluations requested to be done at the Day 28 of Cycle 6) and she/he is eligible to continue the study drug treatment in the long-term study (i.e. Study DSC/11/2357/44), the evaluation performed at the Cycle 6 Day 28 visit of this study can be also counted for the pre-treatment evaluations of the Study DSC/11/2357/44, provided that no difference in the evaluation is present between the two studies (e.g. haematological and biochemical evaluations). **No additional Givinostat study (i.e. Study DSC/12/2357/45)-specific assumption has to be done at the completion of the Day 28 of Cycle 6**. Indeed, in case the patient completes the study (i.e. performs all the evaluations requested to be done at the Day 28 of Cycle 6 of this study), she/he is eligible to continue the study drug treatment in the long-term study (i.e. Study DSC/11/2357/44) and she/he receive the written authorization of the treatment from the Sponsor of their designee (i.e. a patient's confirmation form that includes the patient ID to use into the Study DSC/11/2357/44), the patient will continue the study drug treatment into the Study DSC/11/2357/44, receiving the study (i.e. Study DSC/11/2357/44)-specific drug to be taken.

As reported also in the paragraph 4.3.3, if the patient discontinues for any reason (including discontinuation for pregnancy), with drug related adverse event ongoing at study end, he/she must be followed until resolution or stabilization of the event or until

it is reasonable to consider the event not drug related any more or until the start of a new treatment, whichever occurs first.

If the patient needs to take one of the concomitant medications included in list of "Drugs with risk of Torsades de Pointes" (see Appendix C) the treatment with Givinostat is to be promptly discontinued and the patient must leave the study.

In case of multiple reasons (e.g. patient withdraws the consent for toxicity), "adverse events" should be indicated as the primary reason whenever applicable. All relevant information related to the reason for treatment discontinuation including contributory factors must be included on the 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. Should any drug-related AE still be ongoing beyond the last scheduled visit, this must be followed at subsequent follow-up visits until recovery. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance every effort should 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 must be included on the CRF.

At study close-out, and as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and the completed drug forms to Italfarmaco S.p.A., Dipartimento di Tecnica Farmaceutica, Viale Fulvio Testi, 330, 20126 Milan (MI), Italy, or their designee.

Only in some particular cases, after the authorization of Italfarmaco S.p.A. (or after a signed agreement between the investigational site and Italfarmaco S.p.A.), these materials can be destroyed locally.

4.5.4.2 *Part B*

Appendix A (in particular, paragraph 10.1.2) summarize timing information.

Patients should be told to arrive after an overnight fast of at least 8 hours at all study visits that request a blood test. However, the study visits should still be conducted even if the patient does not adhere to fasting requirements and this will not be considered a protocol violation. In these cases, this information (i.e. not fasting condition) has to be noted by the Investigator in the medical chart and reported in CRF, in order to avoid any misunderstanding of the collected data (e.g. glucose value is influenced by fasting/ not fasting conditions).

If the first ECG evaluation demonstrates 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) must be performed. The averaged value of these three ECG evaluations has to be used for the evaluation of the QTc interval. In the CRF all the performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*.

The spleen evaluation will be performed during the study according to institutional guidelines and site-specific clinical practice (i.e. MRI or CT scan). The same imaging technique and the same instrument should be used on a patient throughout the study, *if possible*. No spleen evaluation will be performed in splenectomised patients.

Patients can take drug at home, except for the first drug administration.

4.5.4.2.1 Pre-treatment evaluations (up to 4 weeks: -28 to Day -1)

The following procedures will be performed at the pre-treatment visit of ***Part B*** as reported below:

- Informed consent signing;
- Demographic data (race, sex and date of birth);
- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
- Medical history;
- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), height, weight, body temperature and ECOG performance status;
- Pregnancy test (*if indicated*);
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN or Urea (as per site-specific clinical practice; see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin, eGFR determination (according with the Mayo Clinic Quadratic Equation);
- ECG, QTc determination (according with Bazett's correction formula);
- Urinalysis: pH, specific gravity, protein, glucose;
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- Spleen evaluation by MRI or CT scan;
- Collection of a blood sample for the quantitative RT-PCR evaluation of $JAK2^{V617F}$ mutational status on peripheral blood (PB) granulocyte;
- Assessment of disease-related symptoms using the MPN-SAF QOL Questionnaire **[24**, **32**];
- Bone marrow histological evaluation, in patients who have consented to this optional exploratory research, who haven't this assessment in the month before the 1 month before the study start (i.e the signature of the Informed Consent

Form, and that have not any medical contraindication to bone marrow sampling as judged by the Investigator);

- Request of enrolment and receipt of patient ID.

Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status [28] ≤ 2 within 7 days of initiating study drug.

The pregnancy test (*if indicated*) has to be 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 must be confirmed with a serum pregnancy test and the result recorded in the CRF.Pre-treatment evaluations will be performed at one or more clinic visit to determine eligibility for the study. Pre-treatment evaluations must be performed up to 4 weeks before the treatment start within **± 7 days**.

Please note that, in case the patient performs the bone marrow histological evaluation as requested by the "**new**" ELN criteria (i.e. the **revised** ELN response criteria) [**33**] (see paragraph 4.8.7) – 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 Informed Consent Form), 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 will be transcribed into the 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, will be monitored and stored at the study site.

In case the patient refuses to provide this written consent to perform the bone marrow evaluation, this patient can be anyway 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 [**33**], and the evaluation of the effect of Givinostat on each single response parameter according to the revised ELN response criteria [**33**]).

If all eligibility criteria are met at the pre-treatment visit, the treatment with Givinostat can start.

After the check that all eligibility criteria are met by the patient and in any case before the treatment start, **all patients with an uncontrolled HCT (i.e. HCT ≥ 45%) have to perform phlebotomy(ies) to normalize the HCT value (i.e. HCT <45%).**

In case of patients who are phlebotomy-dependent, all efforts have to be made by Investigators to record all phlebotomies witch recruited patients experienced at least 6 months before the treatment start.

4.5.4.2.2 Day 1 of Cycle 1

The following procedures must be performed exactly at Day 1 of Cycle 1 of ***Part B*** as reported below:

1) **Pre-dose evaluations:**
   The following procedures will be performed **before the first Givinostat dose** as reported below:
   - Adverse event recording;
   - Concomitant medications (drugs);
   - Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
   - PD sample collection;
   - PK sample collection and preparation, in order to allow to perform both the PK and PD evaluations starting from the same sample [**34**] (*if requested*).
2) **Post-dose evaluations:**
   The following procedures will be performed **after the first Givinostat dose** as reported below:
   - Adverse event recording;
   - Concomitant medications (drugs);
   - Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
   - PD sample collection ***12 hours after the first Givinostat dose***;
   - PK sample collection (2, 3 and 8 hours post-dose) and preparation, in order to allow to perform both the PK and PD evaluations starting from the same sample [**34**] (*if requested*);
   - First Givinostat dose and accountability.

4.5.4.2.3 Day 28 of Cycles 1, 2, 4 and 5

The following procedures will be performed at Day 28 of Cycles 1, 2, 4 and 5 of ***Part B*** (within **± 3 days**) as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);

- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status;
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN or Urea (as per site-specific clinical practice; see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin, eGFR determination (according with the Mayo Clinic Quadratic Equation);
- ECG, QTc determination (according with Bazett's correction formula);
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- Collection of a blood sample for the quantitative RT-PCR evaluation of $JAK2^{V617F}$ mutational status on peripheral blood (PB) granulocyte;
- Used/unused/partially used Givinostat supply return, Givinostat administration and Givinostat accountability;
- ***Only at Cycle 2*:** PK sample collection (pre-dose and 1, 2, 4 and 8 hours post-dose) and preparation, in order to allow to perform both the PK and PD evaluations starting from the same sample [**34**] (*if requested*).

4.5.4.2.4 Day 28 of Cycles 3 and 6

The following procedures will be performed at Day 28 of Cycles 3 and 6 of ***Part B*** (within **± 3 days**) as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status;
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN or Urea (as per site-specific clinical practice; see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin, eGFR determination (according with the Mayo Clinic Quadratic Equation);
- ECG, QTc determination (according with Bazett's correction formula);
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- Spleen evaluation by MRI or CT scan;
- Collection of a blood sample for the quantitative RT-PCR evaluation of $JAK2^{V617F}$ mutational status on peripheral blood (PB) granulocyte;

- Assessment of disease-related symptoms using the MPN-SAF QOL Questionnaire **[24**, **32]**;
- Bone marrow histological evaluation (only for ***cycle 6***) in patients who have consented to this optional exploratory research and that have not any medical contraindication to bone marrow sampling as judged by the Investigator;
- Therapeutic response evaluation according to the clinico-haematological ELN response criteria [**21**] (see paragraph 4.6.1);
- Therapeutic response evaluation according to the "**new**" ELN criteria (i.e. **revised** ELN response criteria) **[33]** (see paragraph 4.8.7) (only for ***cycle 6***);
- ***Only for Cycle 3:*** Givinostat administration;
- Used/unused/partially used Givinostat supply return and Givinostat accountability.

All phlebotomies performed in the first 3 weeks of treatment will be **not** counted to assess the therapeutic response.

4.5.4.2.5 End of study

The following procedures will be performed **at the end of study visit** (in case of completed study) **or 7 days after last drug intake** (in case of the patient drops-out of the study) **(within** ± 3 days**)** as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status;
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN or Urea (as per site-specific clinical practice; see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin, eGFR determination (according with the Mayo Clinic Quadratic Equation);
- ECG, QTc determination (according with Bazett's correction formula);
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- Spleen evaluation by MRI or CT scan;

- Collection of a blood sample for the quantitative RT-PCR evaluation of $JAK2^{V617F}$ mutational status on peripheral blood (PB) granulocyte;
- Assessment of disease-related symptoms using the MPN-SAF QOL Questionnaire **[24**, **32]**;
- Bone marrow histological evaluation, in patients who have consented to this optional exploratory research, and that have not any medical contraindication to bone marrow sampling as judged by the Investigator;
- Therapeutic response evaluation according to the clinico-haematological ELN response criteria [**21**] (see paragraph 4.6.1);
- Therapeutic response evaluation according to the "**new**" ELN criteria (i.e. **revised** ELN response criteria) **[33]** (see paragraph 4.8.7);
- Used/unused/partially used Givinostat supply return and Givinostat accountability.

In case the patient drops-out the study during the first 3 Cycles (i.e. before the Day 28 of Cycle 3), the bone marrow histological evaluation has not to be performed at End of Study visit.

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 the Cycle 6 Day 28 visit can be counted for the End of Study visit.

In addition, in case the patient completes the study (i.e. performs all the evaluations requested to be done at the Day 28 of Cycle 6) and she/he is eligible to continue the study drug treatment in the long-term study (i.e. Study DSC/11/2357/44), the evaluation performed at the Cycle 6 Day 28 visit of this study can be also counted for the pre-treatment evaluations of the Study DSC/11/2357/44, provided that no difference in the evaluation is present between the two studies (e.g. haematological and biochemical evaluations). **No additional Givinostat study (i.e. Study DSC/12/2357/45)-specific assumption has to be done at the completion of the Day 28 of Cycle 6**. Indeed, in case the patient completes the study (i.e. performs all the evaluations requested to be done at the Day 28 of Cycle 6 of this study), she/he is eligible to continue the study drug treatment in the long-term study (i.e. Study DSC/11/2357/44) and she/he receive the written authorization of the treatment from the Sponsor of their designee (i.e. a patient's confirmation form that includes the patient ID to use into the Study DSC/11/2357/44), the patient will continue the study drug treatment into the Study DSC/11/2357/44, receiving the study (i.e. Study DSC/11/2357/44)-specific drug to be taken.

As reported also in the paragraph 4.3.3, if the patient discontinues for any reason (including discontinuation for pregnancy), with drug related adverse event ongoing at study end, he/she must be followed until resolution or stabilization of the event or until it is reasonable to consider the event not drug related any more or until the start of a new treatment, whichever occurs first.

If the patient needs to take one of the concomitant medications included in list of "Drugs with risk of Torsades de Pointes" (see Appendix C) the treatment with Givinostat is to be promptly discontinued and the patient must leave the study.

In case of multiple reasons (e.g. patient withdraws the consent for toxicity), "adverse events" should be indicated as the primary reason whenever applicable. All relevant information related to the reason for treatment discontinuation including contributory factors must be included on the 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. Should any drug-related AE still be ongoing beyond the last scheduled visit, this must be followed at subsequent follow-up visits until recovery. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance every effort should 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 must be included on the CRF.

At study close-out, and as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and the completed drug forms to Italfarmaco S.p.A., Dipartimento di Tecnica Farmaceutica, Viale Fulvio Testi, 330, 20126 Milan (MI), Italy or their designee.

Only in some particular cases, after the authorization of Italfarmaco S.p.A. (or after a signed agreement between the investigational site and Italfarmaco S.p.A.), these materials can be destroyed locally.

4.5.4.3 Information to be collected on screening failures

Patients who sign an informed consent form but who do not start study treatment for any reason will be considered a screen failure. The reason for screen failure and each patient's demographic information will be entered in the CRF within 2 days.

4.6 Efficacy assessments

Appendix A and paragraph 4.5.4 summarize timing information.

4.6.1 Criteria for assessing clinico-haematological improvement

Disease response will be evaluated according to the following clinico-haematological ELN criteria [**21**] (see paragraph 4.6.1) 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 x10^9/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 will be evaluated according to the clinico-haematological ELN and EUMNET criteria [**29**] after 3 and 6 cycles of treatment with Givinostat, in ET and MF patients, respectively.

For ET (from the clinico-hematological 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 will **not** be 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 $x10^9$/L or platelet count increase by ≥ 50% x 10^9/L if baseline < 100 $x10^9$/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 hemoglobin 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 will be evaluated directly by patients according to MPN-SAF QOL questionnaire [**24, 32**].

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

4.6.2 Criteria for determination of MTD

Once all patients enrolled in ***Part A*** have been treated for at least 1 cycle, the study team (see paragraph 4.1.1.2) will 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*.

4.6.3 Criteria for characterization of PK

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

4.6.4 The Efficacy Population

The analysis sets are defined in the paragraph 6.2.1.

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 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*.

4.7 Safety assessments

Safety and tolerability will be 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. Appendix A and paragraph 4.5.4 summarize timing information.

All significant findings already present during the screening visit before drug administration will be reported in the appropriate section of CRF (Medical History section or Current Medical Conditions section). Significant findings occurring after patient enrolment, identified as Adverse Event (AE), will be recorded in Adverse Event section of CRF.

The following criteria will use 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 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).

4.7.1 Laboratory evaluations

The following laboratory examinations (haematology, blood chemistry and urinalysis) will be 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; see Appendix F to convert Urea to BUN) , glucose, Na, K, Ca, Cl, Mg, albumin, eGFR determination (according with the Mayo Clinic Quadratic Equation);
- **Urinalysis:** pH, specific gravity, protein, glucose.

The required amount of blood and urine will be collected at each visit as scheduled above. Appendix A and paragraph 4.5.4 summarize timing information.

All results of laboratory examinations will be entered into the appropriate CRF sections. The original laboratory print-outs will be filed in the patient file at the study site.

Of note, if the ECG evaluation demonstrates 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) must be performed. The averaged value of these three ECG evaluations has to be used for the evaluation of the QTc interval of the related visit. In the CRF all the performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*.

4.7.2 Clinical safety assessments

Clinical safety assessments will include a thorough physical examination, vital signs assessment (respiratory rate, pulse rate and sitting blood pressure will be measured after 5 minutes of rest), weight, body temperature, ECOG performance status, ECG assessment and evaluation, QTc determination (according with Bazett's correction formula, Appendix D).

Appendix A and paragraph 4.5.4 summarize timing information.

All results of the above mentioned clinical safety assessments will be entered into the appropriate CRF sections. The original print-outs related to these evaluations, including the ECG and QTc recording, will be filed in the patient file at the study site.

Of note, if the ECG evaluation demonstrates 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) must be performed. The averaged value of these three ECG evaluations has to be used for the evaluation of the QTc interval of the related visit. In the CRF all the performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*.

4.7.3 Adverse events

All AEs either observed by the Investigator, or reported by the patient spontaneously or in a response to a direct question must be evaluated by the Investigator and will be recorded on the AE section of the CRF.As reported also in the paragraph 4.3.3, if the patient discontinues for any reason (including discontinuation for pregnancy), with drug related adverse event ongoing at study end, he/she must be followed until resolution or stabilization of the event or until it is 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 events" should be indicated as the primary reason whenever applicable. All relevant information related to the reason for treatment discontinuation including contributory factors must be included on the 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. Should any drug-related AE still be ongoing beyond the last scheduled visit, this must be followed at subsequent follow-up visits until recovery. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance every effort should 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 must be included on the CRF.

For AEs definitions, coding and reporting procedures see paragraph 5.

4.8 Exploratory parameters

4.8.1 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 [**21**] (see paragraph 4.6.1) will be 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 will be used to evaluate the effect of Givinostat in ET and MF patients, respectively.

4.8.2 Evaluation of the effects of Givinostat on PD markers

To evaluate the effects of Givinostat on PD markers will be used mRNA analysis.

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.

4.8.3 Spleen size assessment

The spleen evaluation must be performed at the study centre according to the visit schedule outlined in the flow-chart (Appendix A).

To evaluate the effects of Givinostat on spleen size will be used MRI or CT scan.

The spleen evaluation will be 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 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) should be used on a patient throughout the study, *if possible*.

If possible, the spleen dimension will be evaluated as longitudinal diameter (hereafter "A"), antero-posterior diameter (hereafter "B"), transversal diameter (hereafter "C") and Splenic Volumetric Index (hereafter "SVI"):

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

4.8.4 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) will be used in ***Parts A*** and ***B***, in order to assess the most important clinical symptoms among patients with MPNs [**24**].

In addition, starting from MPN-SAF questionnaire, in ***Part B*** also the MPN-SAF Total Symptom Score [**32**] will be assessed as requested by the "**new**" ELN criteria (i.e. **revised** ELN response criteria) [**32**].

4.8.5 Reduction of the JAK2^{V617F} allele burden

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

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.

4.8.6 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 will be used. This assessment will be performed using the data entered by Investigators in the specific section of the CRF.

4.8.7 Evaluation of preliminary efficacy according to the revised ELN criteria

Disease response will be 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*** [**33**].

- ***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 hemorrhagic 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 hemorrhagic 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) [**33**]:

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 [**32**].

4.8.8 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) [**33**] (see paragraph 4.8.7) will be used to evaluate the effect of Givinostat in PV patients in ***Part B***.

4.9 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 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 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) or technical reason.

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

5. ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of AEs as defined in this protocol. AE data will be obtained at all study visits, based on information spontaneously provided by the patient and/or through questioning. Additionally, patients will be advised that they can contact the Investigator at any time to report or discuss AEs.

As reported also in the paragraph 4.3.3, if the patient discontinues for any reason (including discontinuation for pregnancy), with drug related adverse event ongoing at study end, he/she must be followed until resolution or stabilization of the event or until it is 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 events" should be indicated as the primary reason whenever applicable. All relevant information related to the reason for treatment discontinuation including contributory factors must be included on the 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. Should any drug-related AE still be ongoing beyond the last scheduled visit, this must be followed at subsequent follow-up visits until recovery. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance every effort should 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 must be included on the CRF.

5.1 Definitions

5.1.1 Adverse Event (AE)

An Adverse Event is “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment” (ICH E2A).

AEs include:

- Onset of any clinical sign or symptom;
- Worsening (change in nature, severity or frequency) of conditions present at the start of the trial;
- Patient deterioration due to the primary illness;
- Intercurrent illnesses;
- Drug interactions;
- Events related or possibly related to concomitant medications;
- Abnormal laboratory values, as well as significant shifts from baseline within the range of normal, which the investigator considers to be clinically significant.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

5.1.2 Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: “all noxious and unintended responses to a medicinal product related to any dose should be considered Adverse Drug Reaction”.

The phrase "responses to a medicinal products" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Regarding marketed medicinal products, a well-accepted definition of an adverse drug reaction in the post-marketing setting is found in WHO Technical Report 498 [1972] and reads as follows: ”a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.”

The old term "side effect" has been used in various ways in the past, usually to describe negative (unfavourable) effects, but also positive (favourable) effects. It is recommended that this term no longer be used and particularly should not be regarded as synonymous with adverse event or adverse reaction.

5.1.3 Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is "an Adverse Drug Reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational medicinal product or summary of product characteristics, SPC, for marketed products)".

All adverse events judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

5.1.4 Serious Adverse Event (SAE)

A Serious Adverse Event (experience) or reaction is "any untoward medical occurrence that at any dose:

- results is fatal (results in the outcome death);
- is life-threatening*;
- required in-patient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is medically significant or requires intervention to prevent one or other of the outcomes listed above;
- consists in the transmission of an infective agent through the IMP."

**The term life-threatening refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event which hypothetically may cause death if it is more severe.*

Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/ reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.
The pre-planned hospitalization or adverse reaction expected as part of the trial treatment (e.g. standard expected side effect of chemotherapy) should not considered as SAE.
A Suspected Unexpected Serious Adverse Reaction (SUSAR) is referred to an adverse drug reaction which comply with both the definitions of "serious" and "unexpected".

5.2 AE Reporting

The Investigators or their designees are requested to collect and asses any spontaneous AE reported by the patient and to question the patient about AEs and undercurrent illnesses at each visit during the treatment period and any follow-up visit performed to monitor any drug-related AE that is still ongoing beyond the last scheduled visit until recovery. The questioning of patients regarding AEs is generalized such as "*How have you been feeling since your last visit?*" Any AE occurring after a patient has signed the Informed Consent form and up to the follow-up study visit, whether volunteered by the patient, discovered during general questioning by the Investigators or detected through physical examination, laboratory test or other means, will be recorded on the specific section of the CRF. Each AE will be described by:

- *the seriousness;*
- *the duration (start and end dates);*
- *the severity;*
- *the relationship with the IMP;*
- *the action taken.*

The severity of AE should be assessed and graded according to the most recently published NCI Common Terminology Criteria for AE (CTCAE v. 4.03, 14th June 2010).

The relationship with the IMP should be assessed as:

- *related to IMP;*
- *not related to IMP;*
- *unknown.*

The assessment of the relationship of an adverse event with the administration of IMP is a clinical decision based on all available information at the time of the completion of the CRF.

An assessment of "*Not related*" would include the existence of a clear alternative explanation, or non-plausibility.

An assessment of "*Related*" indicates that there is a reasonable suspicion that the adverse event is associated with the use of the IMP.

An assessment "*Unknown*" indicates there is not a reasonable suspicion that the adverse event is associated with the use of the IMP and at the same time there is not the existence of a clear alternative explanation or non-plausibility. In this case, Investigator has to collect all possible information in order to assess the relationship with the IMP, particularly in case of Serious Adverse Events.

Factors to be considered in assessing the relationship of the adverse event to study drug include:

- *The temporal sequence from IMP administration;*
- *The recovery on discontinuation and recurrence on reintroduction;*
- *The concomitant diseases;*

- *The evolution of the treated disease;*
- *The concomitant medication;*
- *The pharmacology and pharmacokinetics of the IMP;*
- *The presence of an alternative explanation*.

5.2.1 Abnormal laboratory findings and other objective measurements

Abnormal laboratory findings and other objective measurements should not be routinely captured and reported as AEs as they will be collected and analysed separately in the CRF. However, abnormal laboratory findings and other objective measurements that meet the criteria for an SAE, result in discontinuation of the IMP or require medical intervention, or are judged by the Investigator to be clinically significant changes from baselines values should be captured and reported on the AE pages of the CRF.

As reported also in the paragraph 4.3.3, if the patient discontinues for any reason (including discontinuation for pregnancy), with drug related adverse event ongoing at study end, he/she must be followed until resolution or stabilization of the event or until it is 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 events" should be indicated as the primary reason whenever applicable. All relevant information related to the reason for treatment discontinuation including contributory factors must be included on the 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. Should any drug-related AE still be ongoing beyond the last scheduled visit, this must be followed at subsequent follow-up visits until recovery. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance every effort should 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 must be included on the CRF.

When reporting an abnormal laboratory finding on the AE pages of the CRF, a clinical diagnosis should be recorded in addition to the abnormal value itself, if this is available (for example "anaemia" in addition to "haemoglobin = 10.5 g/dl").

5.2.2 Baseline medical conditions

Medical conditions present at the screening visit, that do not worsen in severity or frequency during the study are defined as baseline medical conditions and are not AEs. These medical conditions should be adequately documented on the appropriate page of the CRF, i.e. the medical history page. However, medical conditions present at the initial study visit that worsen in severity or frequency during the study should be recorded and reported as AEs.

5.3 SAE Reporting

Any SAE, including death from any cause that occurs after a patient has signed the Informed Consent and up to any follow-up visit performed to monitor any drug-related AE that is still ongoing beyond the last scheduled visit until recovery (regardless of relationship to study drug) must be reported by the Investigators to Italfarmaco S.p.A. within 24 hours of learning of its occurrence.

Related SAEs ***MUST*** be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed. Anyway, no active subject monitoring by the Investigators is required.

The Investigators are required to complete the SAE Form, according with the procedures described in the study manual and within 24 hours of learning of its occurrence. Sufficient details must be provided to allow for a complete medical assessment of the AE and independent determination of possible causality. The Investigators are obliged to pursue and provide additional information as requested by Italfarmaco S.p.A. or their designee(s).

The Investigator must notify the SAE to the Drug Safety Unit (hereinafter "DSU") of Italfarmaco S.p.A. by sending the SAE Form, according with the procedures indicated in the study manual and within 24 hours of learning of its occurrence.

The details of the DSU are specified here below:

Italfarmaco S.p.A.
Drug Safety UnitVia dei Lavoratori, 54
20092 Cinisello Balsamo (MI), Italy
Phone: PPD
Fax: PPD
Fax (back-up): PPD
Mobile: PPD ***e-mail:*** PPD

The same procedure must be applied to the SAE follow-up information.

All serious and unexpected AE that are associated with the use of the study drug (SUSARs) will be notified by Italfarmaco S.p.A. DSU to the competent authority within the required time and following procedures required by applicable laws. It is imperative that Italfarmaco S.p.A. be informed as soon as possible, so that reporting can be done within the required time frame.

The SAEs will also be recorded in the dedicated AE section of the CRF.

5.3.1 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 a SAE, even if no other criteria for seriousness are 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) must be reported to the sponsor within 24 hours and, only in case of AEs, it must 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 will be 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.

5.3.2 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 shall be immediately stopped. The investigator is required to report the pregnancy to Italfarmaco S.p.A. DSU within 24 hours of learning of its occurrence via telephone and/or fax and/or mail (only in case the mail will be automatically generated by the e-CRF). If initially reported via telephone, this must be followed-up with a written report via fax and/or mail (only in case the mail will be automatically generated by the e-CRF) within 24 hours of the telephone report.

Patients should be 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 should be followed until termination, any premature termination should be reported, and the status of the mother and child should be reported to the sponsor after delivery.

If the Investigator is made aware that the partner of a male patient who is participating to the study become pregnant, he/she is required to report the pregnancy to Italfarmaco S.p.A. DSU within 24 hours via telephone and/or fax and/or mail (only in case the mail will be automatically generated by the e-CRF). If initially reported via telephone, this

must be followed-up with a written report via fax and/or mail (only in case the mail will be automatically generated by the e-CRF) within 24 hours of the telephone report.

Whenever possible, such pregnancy should be followed until termination, any premature termination should be reported, and the status of the mother and child should be reported to the sponsor after delivery.

6. STATISTICAL METHODS

6.1 Experimental design

Two-part, multicenter, open label, non-randomized, phase Ib/II study.

6.2 Statistical methods to be employed

Methods here represent the outline of the intended methods.

A Statistical Analysis Plan (SAP) will be produced before the database lock and will contain full details of all planned summaries, listings and analyses.

A standard 3+3 design adopting a modified Fibonacci escalation schema will be used in ***Part A*** [**25**, **26**, **27**].

Sample size for ***Part B*** was discussed for the primary end point defined as the Overall Response Rate after 3 cycles. Simon's 2-stage design will be employed in ***Part B*** [**30**] with the aim of testing the "null hypothesis" that RR ≤ 0.50 versus the "alternative" that RR ≥ 0.75. Response rate will be assessed as defined in paragraph 6.2.5.2. Overall up to 28 patients will need to be recruited, 12 patients being enrolled in Stage-1. PV patients enrolled at the MTD in ***Part A*** may be counted towards Stage 1. Under the "null hypothesis" (if RR = 0.50), the expected total sample size is of 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 favour 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 respond to the treatment the trial will be terminated rejecting the "alternative" that RR $\geq$ 0.75. Otherwise, the trial goes on to Stage-2 enrolling further 16 patients to a total of 28 patients. If at the end of Stage-2, a total of 17 or fewer patients respond to the treatment the "alternative hypothesis" that RR ≥ 0.75 will be rejected; alternatively, if 18 or more patients respond, the "null hypothesis" that RR ≤ 0.50 will be rejected. Estimations are obtained from proprietary software (based on SAS ® 9.2) according to the algorithm proposed by R. Simon [**30**].

Summary statistics will be calculated for all variables. For each continuous variable, the mean, standard deviation, median, minimum value and maximum value will be computed. For each discrete variable the number of patients in each category with non-missing values in relation to all patients with non-missing values of that variable will be provided. Results will be displayed within each cohort and overall, where applicable.

Statistical calculations will be carried-out by resorting to SAS version 9.2 (or later). Both continuous and categorical data will be summarized and tabulated in 2-way tables (variable-by-visit). The main purpose of this phase Ib/II study consists in providing accurate estimates of clinically relevant variables and measures. From the statistical viewpoint this translates in estimating confidence intervals (CIs) with adequate precision where precision represents the degree of uncertainty.

The two tailed 95% CIs of the sample estimates will be computed using parametric approaches if deemed appropriate. Otherwise the StatXact-4 software will be used in order to compute Exact/Nonparametric 95% CIs.

Sub-groups analyses will be performed mainly for exploratory purposes. Since these analyses will be used to promote hypothesis 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.

6.2.1 Analysis Sets

The following analysis sets will be defined:

- Safety analysis set (SAF): The Safety analysis set will include all recruited patients who receive at least one dose of study medication. All safety analyses will be conducted on this population.
- 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. 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.
- Per Protocol analysis set (PP): In order to assess the robustness of the efficacy analysis, the analysis of the efficacy end-point could be repeated in 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.
- MTD analysis set: 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.
- PK Analysis set: will consist of all SAF patients who with at least 1 PK assessment. This analysis set will be used for PK analysis.

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.

6.2.2 Background and demographic characteristics

Demographic data and other baseline characteristics, including medical history, will be analyzed based on safety population. Summary statistics will be provided for all collected variables. For continuous variables, the following statistics will be calculated: mean, standard deviation, median, minimum and maximum values. For discrete variables, the following statistics will be presented: number of patients with non missing values in each category in relation to all patients with non missing values of the respective variable.

Medical history will be listed by patient based on safety population.

6.2.3 IMP

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

In addition, the daily dosage (mg) of Givinostat will be summarized for each patient, and will be summarized descriptively including the mean, standard deviation, median, minimum and maximum.

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

6.2.4 Prior and Concomitant medications and prior and concomitant significant non-drug therapies

Prior medications and significant non-drug therapies (e.g. phlebotomies, transfusions) to treat PV will include regimens discontinued up to 24 weeks prior to enrolment. The information captured will include drug name, start and stop dates, best response to therapy (where applicable) and reason for discontinuations.

Prior medications and prior significant non-drug therapies are defined as those starting and ending prior to the first administration of investigational study drug. Concomitant medications and concomitant significant non-drug therapies are defined as those started at or after first administration of study drug and include those started prior to the first administration of investigational study drug but continued during the study.

Prior and concomitant medications will be classified according to active drug substance using the WHO-DRL drug dictionary (using the most updated version). Frequency tabulations will be presented for prior and concomitant medication by primary therapeutic subgroup (3rd level ATC code), and generic name. Frequency tabulations will be also presented for significant non-drug therapies.

All analyses will be based on safety population.

6.2.5 Primary Efficacy and Safety evaluation

6.2.5.1 *Part A*

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

- 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 most updated version). Adverse events (AEs) will be reported on a per subject basis. If a patient has more than one AE for a treatment that coded to the same preferred term (PT), the patient will be counted only once for that preferred term. Similarly, if a patient has more than one AE for a treatment within a system organ class (SOC) category, the patient will be counted only once in that system organ class category. A patient with multiple CTCAE grades for an AE will be summarized under the maximum CTCAE grade recorded for the event.

Any Adverse Events which started at or after the first administration of study treatment 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 treatment emergent.

An overview of AEs including the number of subjects with at least one AE, at least one TEAE, at least one drug-related TEAE, at least one serious TEAE, any SAE, any AE leading to death, any TEAE leading to death, any TEAE leading to drug discontinuation 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.

6.2.5.2 *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 and PP:

- **For PV and ET** (*if any*)**:** Complete response (CR) and partial response (PR) rate according to clinico-haematological ELN response criteria [**21**] (see paragraph 4.6.1);
- **For MF** (*if any*)**:** Complete response (CR), major response, moderate response and minor response rate according to the EUMNET response criteria (see paragraph 4.6.1).

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 may be expanded to all patients with cMPN.

The clinico-haematological ELN response criteria [**21**] (see paragraph 4.6.1) 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 (see paragraph 4.6.1 for more details).

Frequency and percentage of patients in each response category (complete response (CR), partial response (PR), no response (NR) for PV and ET; Complete response (CR), major response, moderate response and minor response rate for MF) will be presented at each time point. In order to evaluate the response rate, subjects who discontinued prematurely the study for any reason (AE, consent withdrawal, lost to follow up) will be defined as 'Non Responder'. Other missing data will not be replaced, if not otherwise specified.

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:

- 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 most updated version). Adverse events (AEs) will be reported on a per subject basis. If a patient has more than one AE for a treatment that coded to the same preferred term (PT), the patient will be counted only once for that preferred term. Similarly, if a patient has more than one AE for a treatment within a system organ class (SOC) category, the patient will be counted only once in that system organ class category. A patient with multiple CTCAE grades for an AE will be summarized under the maximum CTCAE grade recorded for the event.

Any Adverse Events which started at or after the first administration of study treatment 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 treatment emergent.

TEAE included in this analysis are defined as those starting prior to the date of the first administration of Cycle 4 and include those started prior but continued during the subsequent cycle.

An overview of AEs including the number of subjects with at least one AE, at least one TEAE, at least one drug-related TEAE, at least one serious TEAE, any SAE, any AE leading to death, any TEAE leading to death, any TEAE leading to drug discontinuation 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.

6.2.6 Secondary Efficacy and Safety evaluation

6.2.6.1 *Part A*

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

- Preliminary efficacy of Givinostat (secondary endpoint) for PV/ET and MF patients, respectively (see paragraph 4.6.1 for more details):
  - **For PV and ET** (*if any*)**:** Complete response (CR) and partial response (PR) rate according to the clinico-haematological ELN response criteria [**21**] (see paragraph 4.6.1);
  - **For MF** (*if any*)**:** Complete response (CR), major response, moderate response and minor response rate according to the EUMNET response criteria (see paragraph 4.6.1).

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 may be expanded to all patients with cMPN.

Frequency and percentage of patients in each response category (complete response (CR), partial response (PR), no response (NR) for PV and ET; Complete response (CR), major response, moderate response and minor response rate for MF) will be presented at each time point. In order to evaluate the response rate, subjects who discontinued prematurely the study for any reason (AE, consent withdrawal, lost to follow up) will be

defined as 'Non Responder'. 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 dose cohort along with descriptive statistics.

The PK analysis will be conducted on the PK population.

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. These tables will include number of observations, mean, standard deviation, median, minimum and maximum and additionally the geometric mean and coefficient of variation (not for time to maximum plasma concentration).

6.2.6.2 *Part B*

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

- Preliminary effectiveness of Givinostat (secondary endpoint) after 6 cycles of treatment in ***Part B*** for PV/ET and MF patients, respectively (see paragraph 4.6.1 for more details):
  - **For PV and ET** (*if any*)**:** Complete response (CR) and partial response (PR) rate according to the clinico-haematological ELN response criteria [**21**] (see paragraph 4.6.1);
  - **For MF** (*if any*)**:** Complete response (CR), major response, moderate response and minor response rate according to the EUMNET response criteria (see paragraph 4.6.1).

  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 may be expanded to all patients with cMPN.

  Frequency and percentage of patients in each response category (complete response (CR), partial response (PR), no response (NR) for PV and ET; Complete response (CR), major response, moderate response and minor response rate for MF) will be presented at each time point. In order to evaluate the response rate, subjects who discontinued prematurely the study for any reason (AE, consent withdrawal, lost to follow up) will be defined as 'Non Responder'. 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 the end of Cycles 6, or including data related to Cycles 4, 5 and 6) based on safety population:

- 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 most updated version). Adverse events (AEs) will be reported on a per subject basis. If a patient has more than one AE for a treatment that coded to the same preferred term (PT), the patient will be counted only once for that preferred term. Similarly, if a patient has more than one AE for a treatment within a system organ class (SOC) category, the patient will be counted only once in that system organ class category. A patient with multiple CTCAE grades for an AE will be summarized under the maximum CTCAE grade recorded for the event.

Any Adverse Events which started at or after the first administration of study treatment 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 treatment emergent.

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 subjects with at least one AE, at least one TEAE, at least one drug-related TEAE, at least one serious TEAE, 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 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 (not for time to maximum plasma concentration).

6.2.7 Exploratory evaluations

6.2.7.1 *Parts A* and *B*

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

- The effect of Givinostat on each single response parameter according to the clinico-haematological ELN (for PV and ET) [**21**] (see paragraph 4.6.1) and EUMNET response criteria (for MF); 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 may 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 [**24**, **32**].
- Reduction of the $JAK2^{V617F}$ 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 and PP:

- The preliminary efficacy of Givinostat ***after 6 cycles*** of treatment according to the "**new**" ELN criteria (i.e. **revised** ELN response criteria) [**33**] (see paragraph 4.8.7).
- The effect of Givinostat on single parameters of the "**new**" ELN criteria (i.e. **revised** ELN response criteria) [**33**] (see paragraph 4.8.7).

Explorative endpoints will be summarized by descriptive methods. Default summary statistics and changes from baseline (where applicable) to each time point for all parameters will be produced.

6.2.8 Other Safety evaluation

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 summarized 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.

6.2.9 Interim analyses

Italfarmaco S.p.A. will perform a preliminary analysis of data after the completion of the first cycle of treatment from all patients recruited in ***Part A***, in order to assess the MTD to be used for ***Part B***.

Moreover, a preliminary analysis will be performed on the 12 patients of the first stage of ***Part B***: if six or fewer responses will be observed during the first stage then the study will be stopped; 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***. In this case, a final statistical analysis will be performed considering all patients enrolled in the two study phases.

In addition, Italfarmaco S.p.A. can perform a preliminary analysis of data in case of necessary safety and efficacy updates (e.g. to update regulatory documents and/or the drug safety profile, to revise the development program).

6.3 Sample size and power considerations

A standard 3+3 design adopting a modified Fibonacci escalation schema will be used in ***Part A*** [**25**, **26**, **27**].

Sample size for ***Part B*** was discussed for the primary end point defined as the Overall Response Rate after 3 cycles. Simon's 2-stage design will be employed in ***Part B*** [**30**] with the aim of testing the "null hypothesis" that RR $\leq$ 0.50 versus the "alternative" that RR $\geq$ 0.75. Response rate will be assessed as defined in paragraph 6.2.5.2. Overall up to 28 patients will need to be recruited, 12 patients being enrolled in Stage-1. PV patients enrolled at the MTD in ***Part A*** may be counted towards Stage 1. Under the "null hypothesis" (if RR = 0.50), the expected total sample size is of 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 favour 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 respond to the treatment the trial will be terminated rejecting the "alternative" that RR $\geq$ 0.75. Otherwise, the trial goes on to Stage-2 enrolling further 16 patients to a total of 28 patients. If at the end of Stage-2, a total of 17 or fewer patients respond to the treatment the "alternative hypothesis" that RR $\geq$ 0.75 will be rejected; alternatively, if 18 or more patients respond, the "null hypothesis" that RR $\leq$ 0.50 will be rejected. Estimations are

obtained from proprietary software (based on SAS ® 9.2) according to the algorithm proposed by R. Simon [**30**].

7. ETHICS AND GOOD CLINICAL PRACTICE

The investigator will ensure that this study is conducted in full conformity with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual.

The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline or with local law if it affords greater protection to the subject.

For studies conducted in the EU/EEA countries, the investigator will ensure compliance with the EU Clinical Trial Directive [2001/20/EC] and according to country regulation.

For studies conducted in the USA or under US IND, the investigator will additionally ensure adherence to the basic principles of "GCP" as outlined in the current version of 21 CFR, subchapter D, part 312, "Responsibilities of Sponsors and Investigators", part 50, "Protection of Human Subjects", and part 56, "Institutional Review Boards".

This study will also be carried out in accordance with Italfarmaco S.p.A.'s SOPs.

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of GCP that it conforms to.

7.1 Institutional Review Board/Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to patients, must be reviewed by a properly constituted Institutional Review Board/Ethics Committee (IRB/EC). A signed and dated statement that the protocol and informed consent have been approved by the IRB/EC must be given to Italfarmaco S.p.A. before study initiation. The name and occupation of the chairman and the members of the IRB/EC must be supplied to Italfarmaco S.p.A.. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

7.2 Informed consent

Prior to the beginning of the study, the investigator must have the ECs/IRB written approval/favourable opinion of the written Informed Consent and any other written information to be provided to patients or legally authorized representative. The approved patient information letter/Informed Consent must be filed in the study files (TMF and IF).

Written informed consent must be obtained before any study specific procedure takes place.

The investigator must explain to each patient (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each patient (or legally authorized representative) must be informed that participation in the study is voluntary, that the patient may withdraw from the study at any time for any reason and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The patient (or legally authorized representative) should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If written consent is not possible, oral consent can be obtained if witnessed by a signed statement from one or more persons not involved in the study, mentioning why the patient was unable to sign the form.

8. ADMINISTRATIVE PROCEDURES

8.1 Changes to the protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by Italfarmaco S.p.A..

Amendments can be classified as substantial when impact one of the following criteria:

- The safety or physical or mental integrity of the patient;
- The scientific value of the study;
- The conduct or management of the study;
- The quality or safety of any IMP used in the study.

Substantial amendments require the authorization to the Competent Authority and the positive opinion of the relevant Ethic Committee (EC) before implementation.

In case of urgent safety measures to protect patient against any immediate hazard these measures can be taken without prior authorization from the Competent Authority or favourable opinion of the EC. In this case the Competent Authority and EC will be informed as soon as possible using the fasted means of communication followed by a written report.

Amendments classified as non-substantial require only notification to the ECs involved.

A progress report must be submitted to the EC at required intervals and not less than annually.

At the completion or termination of the study, the study center must submit a close-out letter to the EC and Italfarmaco S.p.A..

8.2 Monitoring procedures

The study will be monitored by a CRO according to GCP guidelines.

A site visit will be held prior to initiation of patient enrolment. The protocol, CRFs, study drug supplies and relevant procedures will be explained to the Investigator's and his/her staff in detail at the site visit. During the study, the study monitor will visit the site regularly, to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to GCP, the progress of enrolment, and also to ensure that study medication is being stored, dispensed and accounted for according to specifications. The investigator and key trial personnel must be available to assist the monitor during these visits.

The investigator must give the monitor access to relevant hospital or clinical records, to confirm their consistency with the CRF entries. No information in these records about the identity of the patients will leave the study centre. Monitoring standard procedures require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs and the recording of primary efficacy and safety variables. The investigator is responsible for completing the CRFs expeditiously to capture all the relevant information, while the monitor is responsible for reviewing them and clarifying any data queries.

8.3 Recording of data and retention of documents

Data on patients collected on CRFs during the trial will be documented in an anonymous fashion and the patient will only be identified by the patient number and by his/her date of birth. All the information required by the protocol should be provided and any omissions require explanation. All CRFs must be completed expeditiously after the patient's visit.

The CRO will provide the study site with electronic CRF and the guidelines for the CRF compilation for each patient.

The investigator must maintain source documents for each patient in the study. All information on CRFs must be traceable to these source documents, which are generally maintained in the patient's file. The source documents should contain all demographic and medical information, including laboratory data, electrocardiograms, etc.

Essential documents of the study must be retained by the investigator for as long as needed to comply with national and international regulations (in Italy at least 7 years).

8.4 Auditing procedures

Italfarmaco S.p.A. reserves the right to conduct auditing activities at any/all participating centres and contracted a CRO or their delegates in order to verify compliance with Italfarmaco S.p.A. internal SOPs, CRO and/or their delegates SOPs, the principles of GCP and all applicable laws. A Regulatory Authority may also wish to conduct an inspection (during the study or even after its completion). If an inspection is requested by a Regulatory Authority, the Investigator must inform Italfarmaco S.p.A. immediately that this request has been made.

8.5 Handling of study medication

All study medication will be supplied to the pharmacy of the Centre by Italfarmaco S.p.A. or its designee. Drug supplies must be kept in an appropriate, secure area and stored in accordance with the conditions specified on the drug labels. The investigator must maintain an accurate record of the shipment and dispensing of the IMP in the drug accountability form. An accurate record of the date and amount of study drug dispensed to each patient must be available for inspection at any time. Copies of the drug accountability form will be provided to Italfarmaco S.p.A. by the investigator.

All drug supplies are to be used only for this protocol and not for any other purpose. The investigator must not destroy any partly-used or unused drug supply without authorization from Italfarmaco S.p.A.. At the conclusion of the study, and, as appropriate during the course of the study, the investigator will return all used and unused drug containers to Italfarmaco S.p.A., Dipartimento di Tecnica Farmaceutica, Viale Fulvio Testi, 330, 20126 Milan (MI), Italy or their designee (e.g. CMO), and a copy of the completed IMP accountability form to the Italfarmaco S.p.A. monitor.

8.6 Ownership of data, disclosure and confidentiality

The investigator must assure that patients' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the sponsor, patients should not be identified by their names, but by an identification code. The investigator should keep an enrolment log showing codes, names and addresses.

By signing the protocol, the Investigator agrees to keep all information provided by Italfarmaco S.p.A. in strict confidence and to request similar confidentiality from his/her staff and the IRB/ECs. Study documents provided by Italfarmaco S.p.A. (protocols, investigators' brochures, CRFs and other material) will be stored appropriately to ensure their confidentiality. The information provided by Italfarmaco S.p.A. to the Investigator may not be disclosed to others without direct written authorization from Italfarmaco S.p.A., except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

Italfarmaco S.p.A assures that the key design items of the Protocol will be published in a publicly accessible database such as "Clinicaltrials.gov". Moreover, upon completion of the Study and finalization of the Study report, the Results of these study will be submitted for publication or posted in a publicly accessible data base.

By signing the protocol, the investigators and their co-workers accept to submit any intended communication (abstract, paper or oral presentation) to Italfarmaco S.p.A. reasonably in advance (at least 30 working days for an abstract or oral presentation and 60 working days for a manuscript). This is to allow Italfarmaco S.p.A. to review the communications for accuracy and confidentiality, to provide any relevant supplementary information and to allow establishment of co-authorship and in no way

has to be intended as a restriction of the sponsor to the investigators' right to publish the results of the study. In case Italfarmaco S.p.A. identifies specific need/opportunity to patent any of the study findings, the Investigator will allow a six month time-window between his submission to Italfarmaco S.p.A. and the intended publication and actual submission/communication to third parties, in order to allow Italfarmaco S.p.A. to undertake appropriate patenting steps.

8.7 Study discontinuation

Italfarmaco S.p.A. has the right to terminate this study at any time. Reasons for terminating the study may include the following:

- unsatisfactory patient enrolment;
- inaccurate or incomplete quality or quantity of data recording;
- incidence or severity of adverse drug reactions in this or other studies with Givinostat indicating a potential health hazard to patients;
- poor adherence to protocol and regulatory requirements;
- plans to modify or discontinue the development of the study drug.

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10. APPENDICES

Appendix A: Flow-chart

Appendix B: ECOG performance status table

Appendix C: Drugs at risk of causing TdP

Appendix D: Bazett's correction formula

Appendix E: $JAK2^{V617F}$ genotyping and quantification in granulocytes

Appendix F: Conversion Formula (from Urea to BUN)

10.1 Appendix A: Flow-chart

10.1.1 Flow-chart of *Part A*

10.1.1.1 Flow-chart of Cycle 1

Cycle Description	**Screening**	**Cycle 1**										
Cycle Day	**-28 to Day -1**	**Day 1**		**Day 2**	**Day 3**	**Day 4**	**Day 8**	**Day 10**	**Day 15**	**Day 22**	**Day 28**	**EOS[11]**
Treatment phase	**Pre-dose**	**Pre-dose**	**Post-dose**	**TREATMENT**								
Window	**± 7 days**	**Not applicable**					**± 3 days**					
Visit at the investigational site	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Informed Consent Form signature	**X**											
Demographic data	**X**											
Adverse event recording	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Concomitant medications (drugs)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Non-drug therapies (e.g. phlebotomies, transfusions)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Medical history	**X**											
Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), height, weight, body temperature and ECOG performance status[1]	**X**			**X**			**X**		**X**	**X**	**X**	**X**
Physical examination, weight, body temperature and ECOG performance status		**X**										
Vital signs (blood pressure, pulse rate, respiratory rate)		**X**										
Vital signs (blood pressure, pulse rate, respiratory rate) ***4 hours after the first Givinostat dose***			**X**									

Cycle Description	**Screening**	**Cycle 1**										
Cycle Day	**-28 to Day -1**	**Day 1**		**Day 2**	**Day 3**	**Day 4**	**Day 8**	**Day 10**	**Day 15**	**Day 22**	**Day 28**	**EOS[11]**
Treatment phase	**Pre-dose**	**Pre-dose**	**Post-dose**	**TREATMENT**								
Window	**± 7 days**	**Not applicable**					**± 3 days**					
Visit at the investigational site	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Pregnancy test (*if indicated*) [2]	**X**											
Blood chemistry[3]	**X**	**X**					**X**		**X**	**X**	**X**	**X**
ECG, QTc determination (according with Bazett's correction formula) ***3 hours after the first Givinostat dose***[12]			**X**									
ECG, QTc determination (according with Bazett's correction formula)[12]	**X**	**X**		**X**			**X**		**X**	**X**	**X**	**X**
Urinalysis[4]	**X**										**X**	**X**
Haematology[5]	**X**						**X**		**X**	**X**	**X**	**X**
PD sample collection*		**X**										
PD sample collection ***12 hours after the first Givinostat dose*** *			**X**									
PK sample collection and preparation, in order to allow to perform both the PK and PD evaluations starting from the same sample[6,*]		**X**	**X**								**X**	
Spleen evaluation (by MRI or CT scan)[7]	**X**											**X**
Therapeutic response evaluation [8]												**X**
Collection of a blood sample for the quantitative RT-PCR evaluation of $JAK2^{V617F}$ mutational status on peripheral blood (PB) granulocyte*	**X**											

Cycle Description	**Screening**	**Cycle 1**										
Cycle Day	**-28 to Day -1**	**Day 1**		**Day 2**	**Day 3**	**Day 4**	**Day 8**	**Day 10**	**Day 15**	**Day 22**	**Day 28**	**EOS[11]**
Treatment phase	**Pre-dose**	**Pre-dose**	**Post-dose**	**TREATMENT**								
Window	**± 7 days**	**Not applicable**					**± 3 days**					
Visit at the investigational site	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Assessment of disease-related symptoms using the MPN-SAF QOL Questionnaire	**X**											**X**
Request of enrolment and receipt of patient ID	**X**											
First Givinostat dose and accountability			**X**									
Givinostat administration and accountability[9]				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Used/unused/partially used Givinostat supply return from patient(s) and Givinostat accountability[10]				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

[1] ***Height*** **<u>will be measured at the pre-treatment evaluations only.</u>**
<u>Patients must have an ECOG ≤ 1 within 7 days of initiating study drug.</u>

[2] ***Pregnancy test*** **<u>has to be performed within 72 hours before the first Givinostat dose</u>**. The test can be performed by urine or serum pregnancy test. In case of a borderline-positive urine pregnancy test, this must be confirmed with a serum pregnancy test.

[3] ***Blood Chemistry***: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN or Urea (according with the site-specific clinical practice), glucose, Na, K, Ca, Cl, Mg, albumin, eGFR determination (according with the Mayo Clinic Quadratic Equation).

[4] ***Urinalysis***: pH, specific gravity, protein, glucose.

[5] ***Haematology***: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count.

[6] ***PK sample collection***: as following summarize:

- **<u>Day 1</u>**: pre-dose and 2, 3 and 8 hours post-dose;
- **<u>Day 28</u>**: pre-dose and 1, 2, 4 and 8 hours post-dose.

Patients will not take the morning dose of Givinostat on the day selected for their timed PK assessments. Study drug will be 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 will take the morning dose of study drug prior to the visit.

[7] ***Spleen evaluation as per site-specific clinical practise***: Patients with splenomegaly will be followed according to institutional guidelines (i.e. MRI or CT scan). The same imaging technique and the same instrument should be used on a patient throughout the study, if possible. No spleen evaluation will be performed in splenectomised patients.

[8] ***Therapeutic response evaluation***: for PV and ET (*if any*), according with the clinico-haematological ELN response criteria [**21**] (see paragraph 4.6.1); for MF (*if any*), according with EUMNET response criteria.

[9] ***Givinostat administration***: patients can take drug at home, except for the first drug administration.

[10] ***IMP***: at study close-out, and **as appropriate during the course of the study**, the Investigator will return all used and unused study drug, packaging, drug labels, and the completed drug forms to Italfarmaco S.p.A., Dipartimento di Tecnica Farmaceutica, Viale Fulvio Testi, 330, 20126, Milan (MI), Italy or their designee (e.g. CMO).

Only in some particular cases, after the authorization of Italfarmaco S.p.A. (or after a signed agreement between the investigational site and Italfarmaco S.p.A.), these materials can be destroyed locally.

[11] ***EOS:*** In case of the patient drops-out of the study, the end of Study (EOS) visit will be performed 7 days after last drug intake.

Note that, as reported in the paragraph 4.3.3, if the patient discontinues for any reason (including discontinuation for pregnancy), with drug related adverse event ongoing at study end, he/she must be followed until resolution or stabilization of the event or until it is 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 events" should be indicated as the primary reason whenever applicable. All relevant information related to the reason for treatment discontinuation including contributory factors must be included on the 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. Should any drug-related AE still be ongoing beyond the last scheduled visit, this must be followed at subsequent follow-up visits until recovery. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance every effort should 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 must be included on the CRF.

[12] ***ECG***: If the ECG evaluation demonstrates a prolonged QTc interval (i.e. a QTc interval $\geq$ 450 msec), two additional ECG evaluations over a brief period of time (i.e. 5 minutes between each recording) must be performed. The averaged value of these three ECG evaluations has to be used for the evaluation of the QTc interval. In the CRF all the performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*.

[*] For all time points a blood sample will be collected as back-up sample.

10.1.1.2 Flow-chart of Cycle 2 and beyond

	Day 1 of each cycle	**Day 28 of cycles 2, 4 and 5**	**Day 28 of cycles 3 and 6**	**End of study visit** (in case of completed study) **or 7 days after last drug intake** (in case of the patient drops-out of the study)[8]
Treatment phase	**TREATMENT**			
Window	**± 3 days**			
Visit at the investigational site		**X**	**X**	**X**
Adverse event recording		**X**	**X**	**X**
Concomitant medications (drugs)		**X**	**X**	**X**
Non-drug therapies (e.g. phlebotomies, transfusions)		**X**	**X**	**X**
Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status		**X**	**X**	**X**
Blood chemistry[1]		**X**	**X**	**X**
ECG, QTc determination (according with Bazett's correction formula)[9]		**X**	**X**	**X**
Haematology[2]		**X**	**X**	**X**
PK sample collection and preparation, in order to allow to perform both the PK and PD evaluations starting from the same sample [3, *]		**X**	**X**	
Spleen evaluation (by MRI or CT scan)[4]			**X**	**X**
Therapeutic response evaluation[5]			**X**	**X**
Collection of a blood sample for the quantitative RT-PCR evaluation of $JAK2^{V617F}$ mutational status on peripheral blood (PB) granulocyte [*]			**X**	**X**
Assessment of disease-related symptoms using the MPN-SAF QOL Questionnaire			**X**	**X**
Givinostat administration[6]	**X**	**X**	**X**[10]	
First Givinostat dose of the related cycle and accountability	**X**			

	Day 1 of each cycle	Day 28 of cycles 2, 4 and 5	Day 28 of cycles 3 and 6	End of study visit (in case of completed study) or 7 days after last drug intake (in case of the patient drops-out of the study)8
Treatment phase	**TREATMENT**			
Window	**± 3 days**			
Visit at the investigational site		**X**	**X**	**X**
Used/unused/partially used Givinostat supply return from patient(s) and accountability[7]		**X**	**X**	**X**

[1] ***Blood Chemistry***: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN or Urea (according with the site-specific clinical practice), glucose, Na, K, Ca, Cl, Mg, albumin, eGFR determination (according with the Mayo Clinic Quadratic Equation).

[2] ***Haematology***: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count.

[3] ***PK sample collection:*** pre-dose. Patients will not take the morning dose of Givinostat on the day selected for their timed PK assessments. Study drug will be 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 will take the morning dose of study drug prior to the visit.

[4] ***Spleen evaluation as per site-specific clinical practise***: Patients with splenomegaly will be followed according to institutional guidelines (i.e. MRI or CT scan). The same imaging technique and the same instrument should be used on a patient throughout the study, if possible. No spleen evaluation will be performed in splenectomised patients.

[5] ***Therapeutic response evaluation***: for PV and ET (*if any*), according with the clinico-haematological ELN criteria [**21**] (see paragraph 4.6.1); for MF (*if any*), according with EUMNET response criteria.

[6] ***Givinostat administration***: patients can take drug at home.

[7] ***IMP***: at study close-out, and **as appropriate during the course of the study**, the Investigator will return all used and unused study drug, packaging, drug labels, and the completed drug forms to Italfarmaco S.p.A., Dipartimento di Tecnica Farmaceutica, Viale Fulvio Testi, 330, 20126, Milan (MI), Italy or their designee (e.g. CMO). Only in some particular cases, after the authorization of Italfarmaco S.p.A. (or after a signed agreement between the investigational site and Italfarmaco S.p.A.), these materials can be destroyed locally.

[8] ***EOS:*** as reported in the paragraph 4.3.3, if the patient discontinues for any reason (including discontinuation for pregnancy), with drug related adverse event ongoing at study end, he/she must be followed until resolution or stabilization of the event or until it is 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 events" should be indicated as the primary reason whenever applicable. All relevant information related to the reason for treatment discontinuation including contributory factors must be included on the 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. Should any drug-related AE still be ongoing beyond the last

scheduled visit, this must be followed at subsequent follow-up visits until recovery. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance every effort should 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 must be included on the CRF.

Of note, 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 the Cycle 6 Day 28 visit can be counted for the End of Study visit.

In addition, in case the patient completes the study (i.e. performs all the evaluations requested to be done at the Day 28 of Cycle 6) and she/he is eligible to continue the study drug treatment in the long-term study (i.e. Study DSC/11/2357/44), the evaluation performed at the Cycle 6 Day 28 visit of this study can be also counted for the pre-treatment evaluations of the Study DSC/11/2357/44, provided that no difference in the evaluation is present between the two studies (e.g. haematological and biochemical evaluations). **No additional Givinostat study (i.e. Study DSC/12/2357/45)-specific assumption has to be done at the completion of the Day 28 of Cycle 6**. Indeed, in case the patient completes the study (i.e. performs all the evaluations requested to be done at the Day 28 of Cycle 6 of this study), she/he is eligible to continue the study drug treatment in the long-term study (i.e. Study DSC/11/2357/44) and she/he receive the written authorization of the treatment from the Sponsor of their designee (i.e. a patient's confirmation form that includes the patient ID to use into the Study DSC/11/2357/44), the patient will continue the study drug treatment into the Study DSC/11/2357/44, receiving the study (i.e. Study DSC/11/2357/44)-specific drug to be taken.

[9] ***ECG***: If the ECG evaluation demonstrates 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) must be performed. The averaged value of these three ECG evaluations has to be used for the evaluation of the QTc interval. In the CRF all the performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*.

[10] ***Givinostat administration***: Only for ***cycle 3***.

[*] For all time points a blood sample will be collected as back-up sample.

10.1.2 Flow-chart of *Part B*

	Pre-treatment evaluations[***] (up to 4 weeks: -28 to Day -1)	**Day 1 of the first Cycle**[***]		**Day 28 of Cycles 1, 2, 4 and 5**[***]	**Day 28 of Cycles 3 and 6**[***]	**End of study visit** (in case of completed study) **or 7 days after last drug intake** (in case of the patient drops-out of the study)[11, ***]
Treatment phase	**Pre-dose**	**Pre-dose**	**Post-dose**	**TREATMENT**		
Windows	**± 7 days**	**Not applicable**		**± 3 days**		
Visit at the investigational site	**X**	**X**	**X**	**X**	**X**	**X**
Informed Consent Form signature	**X**					
Demographic data	**X**					
Adverse event recording	**X**	**X**	**X**	**X**	**X**	**X**
Concomitant medications (drugs)	**X**	**X**	**X**	**X**	**X**	**X**
Non-drug therapies (e.g. phlebotomies, transfusions)	**X**	**X**	**X**	**X**	**X**	**X**
Medical history	**X**					
Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), height, weight, body temperature and ECOG performance status[1]	**X**			**X**	**X**	**X**
Pregnancy test (*if indicated*) [2]	**X**					
Blood chemistry[3]	**X**			**X**	**X**	**X**
ECG, QTc determination (according with Bazett's correction formula)[12]	**X**			**X**	**X**	**X**
Urinalysis[4]	**X**					
Haematology[5]	**X**			**X**	**X**	**X**
PD sample collection before the first Givinostat dose [*]		**X**				
PD sample collection 12 hours after the first Givinostat dose [*]			**X**			
PK sample collection[6, *] and preparation, in order to allow to perform both the PK and PD evaluations starting from the same sample (*if requested*)		**X**	**X**	**X**		

	Pre-treatment evaluations (up to 4 weeks: -28 to Day -1)***	**Day 1 of the first Cycle*** **		**Day 28 of Cycles 1, 2, 4 and 5**	**Day 28 of Cycles 3 and 6**	**End of study visit** (in case of completed study) **or 7 days after last drug intake** (in case of the patient drops-out of the study)[11]
Treatment phase	**Pre-dose**	**Pre-dose**	**Post-dose**	**TREATMENT**		
Windows	**± 7 days**	**Not applicable**		**± 3 days**		
Visit at the investigational site	**X**	**X**	**X**	**X**	**X**	**X**
Spleen evaluation (by MRI or CT scan)[7]	**X**				**X**	**X**
Collection of blood sample for quantitative RT-PCR evaluation of $JAK2^{V617F}$ mutational status on peripheral blood (PB) granulocyte *	**X**			**X**	**X**	**X**
Assessment of disease-related symptoms using the MPN-SAF QOL Questionnaire [**24**, **32**]	**X**				**X**	**X**
Bone marrow histological evaluation in order to assess the presence of age adjusted normocellularity and/or trilinear hyperplasia[A]	**X**				**X**[B]	**X**[C]
Therapeutic response evaluation[8]					**X**	**X**
Request of enrolment and receipt of patient ID	**X**					
Givinostat administration[9]				**X**	**X****	
First Givinostat dose and accountability			**X**			
Used/unused/partially used Givinostat supply return from patient(s) and accountability[10]				**X**	**X**	**X**

[1] ***Height*** **will be measured at the pre-treatment evaluations only.**
Patients must have an ECOG ≤ 2, within 7 days of initiating study drug.

[2] ***Pregnancy test*** **has to be performed within 72 hours before the first Givinostat dose**. The test can be performed by urine or serum pregnancy test. In case of a positive or borderline-positive urine pregnancy test, this must be confirmed with a serum pregnancy test.

[3] ***Blood Chemistry***: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN or Urea (according with the site-specific clinical practice), glucose, Na, K, Ca, Cl, Mg, albumin, eGFR determination (according with the Mayo Clinic Quadratic Equation).

[4] ***Urinalysis***: pH, specific gravity, protein, glucose.

[5] ***Haematology***: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count.

[6] ***PK sample collection***: as following summarize:

- **Day 1 of Cycle 1**: pre-dose and 2, 3 and 8 hours post-dose;
- **Day 28 only of Cycle 2**: pre-dose and 1, 2, 4 and 8 hours post-dose.

Patients will not take the morning dose of Givinostat on the day selected for their timed PK assessments. Study drug will be 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 will take the morning dose of study drug prior to the visit.

[7] ***Spleen evaluation as per site-specific clinical practise***: The spleen evaluation will be performed during the study according to institutional guidelines and site-specific clinical practice (i.e. MRI or CT scan). The same imaging technique and the same instrument should be used on a patient throughout the study, *if possible*. No spleen evaluation will be performed in splenectomised patients.

[8] ***Therapeutic response evaluation***: both according with the clinico-haematological ELN criteria [**21**] (see paragraph 4.6.1) (***both at cycle 3 and at cycle 6***) and according with the "**new**" ELN criteria (i.e. **revised** ELN response criteria) [**33**] (see paragraph 4.8.7) (***only at cycle 6)***.

[9] ***Givinostat administration***: patients can take drug at home, except for the first drug administration.

[10] ***IMP***: at study close-out, and **as appropriate during the course of the study**, the Investigator will return all used and unused study drug, packaging, drug labels, and the completed drug forms to Italfarmaco S.p.A., Dipartimento di Tecnica Farmaceutica, Viale Fulvio Testi, 330, 20126 Milan (MI), Italy or their designee (e.g. CMO).

Only in some particular cases, after the authorization of Italfarmaco S.p.A. (or after a signed agreement between the investigational site and Italfarmaco S.p.A.), these materials can be destroyed locally.

[11] ***EOS:*** as reported in the paragraph 4.3.3, if the patient discontinues for any reason (including discontinuation for pregnancy), with drug related adverse event ongoing at study end, he/she must be followed until resolution or stabilization of the event or until it is 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 events" should be indicated as the primary reason whenever applicable. All relevant information related to the reason for treatment discontinuation including contributory factors must be included on the 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. Should any drug-related AE still be ongoing beyond the last scheduled visit, this must be followed at subsequent follow-up visits until recovery. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance every effort should 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 must be included on the CRF.

Of note, 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 the Cycle 6 Day 28 visit can be counted for the End of Study visit.

In addition, in case the patient completes the study (i.e. performs all the evaluations requested to be done at the Day 28 of Cycle 6) and she/he is eligible to continue the study drug treatment in the long-term study (i.e. Study DSC/11/2357/44), the evaluation performed at the Cycle 6 Day 28 visit of this study can be also counted for the pre-treatment evaluations of the Study DSC/11/2357/44, provided that no difference in the evaluation is present between the two studies (e.g. haematological and biochemical

evaluations). **No additional Givinostat study (i.e. Study DSC/12/2357/45)-specific assumption has to be done at the completion of the Day 28 of Cycle 6**. Indeed, in case the patient completes the study (i.e. performs all the evaluations requested to be done at the Day 28 of Cycle 6 of this study), she/he is eligible to continue the study drug treatment in the long-term study (i.e. Study DSC/11/2357/44) and she/he receive the written authorization of the treatment from the Sponsor of their designee (i.e. a patient's confirmation form that includes the patient ID to use into the Study DSC/11/2357/44), the patient will continue the study drug treatment into the Study DSC/11/2357/44, receiving the study (i.e. Study DSC/11/2357/44)-specific drug to be taken.

[12] ***ECG***: If the ECG evaluation demonstrates 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) must be performed. The averaged value of these three ECG evaluations has to be used for the evaluation of the QTc interval. In the CRF all the performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*.

[*] For all time points a blood sample will be collected as back-up sample.

[**] Only for ***cycle 3***.

[***] **Patients should be told to arrive after an overnight fast of at least 8 hours at all study visits that request a blood test.** However, the study visits should still be conducted even if the patient does not adhere to fasting requirements and this will not be considered a protocol violation. In these cases, this information (i.e. not fasting condition) has to be noted by the Investigator in the medical chart and reported in CRF, in order to avoid any misunderstanding of the collected data (e.g. glucose value is influenced by fasting/not fasting conditions).

[A] Please note that, in case the patient performs the bone marrow histological evaluation as requested by the "**new**" ELN criteria (i.e. the **revised** ELN response criteria) [**33**] (see paragraph 4.8.7) – 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 Informed Consent Form), 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 will be transcribed into the 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, will be monitored and stored at the study site.

Finally, in case the patient refuses to provide this written consent to perform the bone marrow evaluation, this patient can be anyway 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 [**33**], and the evaluation of the effect of Givinostat on each single response parameter according to the revised ELN response criteria [**33**]).

[B] Only for ***cycle 6***.

[C] In case the patient drops-out the study during the first 3 Cycles (i.e. before the Day 28 of Cycle 3) , this evaluation has not to be performed at End of Study visit.

10.2 Appendix B: ECOG Performance Status*

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

** As published in Am. J. Clin. Oncol (1982).*

10.3 Appendix C: Drugs at risk of causing TdP

Drugs that are generally accepted by the Scientific Advisory Board of the AZCERT to have a risk of causing Torsades de Pointes.

Generic Name	List
Amiodarone	Anti-arrhythmic / abnormal heart rhythm
Amiodarone	Anti-arrhythmic / abnormal heart rhythm
Arsenic trioxide	Anti-cancer / Leukemia
Astemizole	Antihistamine / Allergic rhinitis
Azithromycin	Antibiotic / bacterial infection
Bepridil	Anti-anginal / heart pain
Chloroquine	Anti-malarial / malaria infection
Chlorpromazine	Anti-psychotic/ Anti-emetic / schizophrenia/ nausea
Cisapride	GI stimulant / heartburn
Citalopram	Anti-depressant / depression
Clarithromycin	Antibiotic / bacterial infection
Disopyramide	Anti-arrhythmic / abnormal heart rhythm
Dofetilide	Anti-arrhythmic / abnormal heart rhythm
Domperidone	Anti-nausea / nausea
Droperidol	Sedative;Anti-nausea / anesthesia adjunct, nausea
Erythromycin	Antibiotic;GI stimulant / bacterial infection; increase GI motility
Erythromycin	Antibiotic;GI stimulant / bacterial infection; increase GI motility
Flecainide	Anti-arrhythmic / abnormal heart rhythm
Halofantrine	Anti-malarial / malaria infection
Haloperidol	Anti-psychotic / schizophrenia, agitation
Ibutilide	Anti-arrhythmic / abnormal heart rhythm
Levomethadyl	Opiate agonist / pain control, narcotic dependence
Mesoridazine	Anti-psychotic / schizophrenia
Methadone	Opiate agonist / pain control, narcotic dependence
Methadone	Opiate agonist / pain control, narcotic dependence
Moxifloxacin	Antibiotic / bacterial infection
Pentamidine	Anti-infective / pneumocystis pneumonia
Pentamidine	Anti-infective / pneumocystis pneumonia
Pimozide	Anti-psychotic / Tourette's tics
Probucol	Antilipemic / Hypercholesterolemia
Procainamide	Anti-arrhythmic / abnormal heart rhythm
Procainamide	Anti-arrhythmic / abnormal heart rhythm

Quinidine	Anti-arrhythmic / abnormal heart rhythm
Quinidine	Anti-arrhythmic / abnormal heart rhythm
Sotalol	Anti-arrhythmic / abnormal heart rhythm
Sparfloxacin	Antibiotic / bacterial infection
Terfenadine	Antihistamine / Allergic rhinitis
Thioridazine	Anti-psychotic / schizophrenia
Vandetanib	Anti-cancer / Thyroid cancer

Source: www.azcert.org/medical-pros/drug-lists/pubMed-drug-list.cfm

Revised: 17/05/2012

Arizona Center for Education and Research on Therapeutics (AZCERT)
The Critical Path Institute
Tucson, Arizona and Rockville, Maryland

10.4 Appendix D: Bazett's correction formula

BAZETT'S CORRECTION FORMULA

$$QTc = QT / RR^{0.5}$$

RR = interval from the onset of one QRS complex to the onset of the next QRS complex, measured in seconds.

10.5 Appendix E: $JAK2^{V617F}$ genotyping and quantification in granulocytes

$JAK2^{V617F}$ genotyping and quantification will be performed in ***Part A*** at the screening, at Day 28 of Cycle 3, at Day 28 of Cycle 6 and at the end of study, and in ***Part B*** at the screening, at Day 28 of each Cycle (i.e. Day 28 of the Cycles 1, 2, 3, 4, 5 and 6) and at the end of study. A sample of peripheral blood in EDTA (20 mL) will be obtained, and either granulocyte are separated in the same institution up to the freezing of a granulocyte pellet, or the blood sample is sent the same day with an O/N courier to the Central Laboratory. Granulocytes are prepared from peripheral blood (PB) samples using density-gradient centrifugation and residual erythrocyte lyses; granulocytes are frozen as a pellet. Frozen pellets from different patients can be sent in blocks to the Central Laboratory in dry ice. DNA is extracted using solid-phase extraction. The presence and the mutation, and the allelic burden, are evaluated in triplicate in each sample, using a quantitative real-time PCR (RT-PCR) technique and standard curve with plasmids available the Central Laboratory [**31**].

10.6 Appendix F: Conversion formula (from Urea to BUN)

CONVERSION FORMULA (FROM UREA TO BUN)

BUN (mg/dL) = [Urea (mg/dL)] / 2.14

CRO SIGNATURES

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10AUG 2015
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STUDY N.: DSC/12/2357/45

EUDRACT N.: 2013-000860-27

A two-part study to assess the safety and preliminary efficacy of Givinostat in patients with JAK2^{V617F} positive Polycythemia Vera

Document type:	Amendment 2	
Development Phase:	Phase Ib/II	
Document status:	Version 1.0	Release: 29th July 2015

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Amendment 2
Version 1.0 – 29th July 2015

AMENDMENT 2 RATIONALE

The clinical study protocol DSC/12/2357/45 version 2.0 (including Amendment 1, version 1.0, 23rd July 2013) has been amended for the following reasons:

- To update the safety sections according to the current notification of SAE Form (i.e. by eCRF), Adverse Events definition and the details of the Drug Safety Unit.
- To amend some wording in the *preclinical rationale* (paragraph 1.3) based on the most updated information.
- To update the approved drugs for the treatment of Polycythemia Vera and Myelofibrosis, based on the current data.
- To add the neuromuscular disorders in the indications explored with Givinostat.
- To clarify that is necessary that the long-term study (Study N.: DSC/11/2357/44) has already received all necessary approvals in that specific country and site, and that the study was initiated in that particular site, in order to allow patients achieving clinical benefit to continue treatment with Givinostat (at the same dose and schedule) after completion of the study DSC/12/2357/45.
- To update the sections related to ***Part B***, based on the definition of the MTD of Givinostat as chronic treatment in Polycythemia Vera patients, now available.

  Of note, on 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., hereinafter "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 Polycythemia Vera 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 Dose Levels 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 is a chronic treatment for PV patients in the current schedule;
  - The observed PLTs decrease;

- The knowledge of the safety profile of HDACi and, in particular, of Givinostat (i.e. thrombocythopenia is a side-effect);
- It could be preferable/ethical to avoid to expose 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., is the MTD of Givinostat defined taking into account the chronic schedule of the study drug as prescribed in this current study.

- To update 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 chronic myeloproliferative neoplasms. 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.
  Of note, the same dose modification criteria may be followed also by patients initially dosed at lower dose levels in ***Part A*** that, after the definition of MTD, are 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.

- To add the Contract Manufacturing Organization as possible delegate for the management of the study drug (e.g. secondary packaging, distribution to the sites).

- To clarify the meaning of "***any other investigational drug or device***" (i.e. exclusion criterion n. 19).

- To add the strength of 75 mg.

- To add some clarifications in the instructions related to the study administration and dispensing.

- To add pharmacodynamic evaluations that will be performed using an aliquot of the PK samples.

- To specify the calculation of eGFR (i.e. a derived biochemical parameter) according with the Mayo Clinic Quadratic Equation, as agreed with the German Regulatory Authority.

- To clarify that it is allowed the evaluation of Urea (in spite of BUN) according with the the site-specific clinical practice.

- To add 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).

- To clarify that no spleen evaluation will be performed in splenectomised patients, while the spleen evaluation is requested in all other patients in ***Part B***, since the presence of splenomegaly is one of the parameter to evaluate as per primary objectives of ***Part B*** (i.e. according to the ELN response criteria).

- To specify 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 request a blood test.

- To add the collection of a blood sample for the quantitative RT-PCR evaluation of $JAK2^{V617F}$ mutational status on peripheral blood (PB) granulocyte at the following visits of ***Part B***: Day 28 of Cycles 1, 2, 4 and 5.

- To clarify that, 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 the Cycle 6 Day 28 visit can be also counted for the End of Study visit.

- To specify that, in case the patient completes the study (i.e. performs all the evaluations requested to be done at the Day 28 of Cycle 6) and she/he is eligible to continue the study drug treatment in the long-term study (i.e. Study DSC/11/2357/44), the evaluation performed at the Cycle 6 Day 28 visit of this study can be also counted for the pre-treatment evaluations of the Study DSC/11/2357/44, provided that no difference in the evaluation is present between the two studies (e.g. haematological and biochemical evaluations).

- To clarify that all efficacy analyses will be conducted on this population and will be based on the effective DL/daily doses of Givinostat at which each patient has been treated.

Further to what is reported above, with the present amendment some typographic mistakes existing in the clinical study protocol version 2.0 (including Amendment 1, version 1.0, 23rd July 2013) have been put right. In addition, with the present amendment some sentences existing in the clinical study protocol version 2.0 (including Amendment 1, version 1.0, 23rd July 2013) have been clarified in order to better detail the right procedures to be followed.

AMENDMENT 2 SUMMARY OF CHANGES

Substantive additions to the protocol are denoted in **bold**. Substantive deletions are in ~~strikethrough~~.

EMERGENCY SAFETY PROCEDURES

Any SAE (see chapter "Adverse Events" for definition and details), that occurs after a patient has signed the Informed Consent **Form** and up to the follow-up visit (regardless of relationship to study drug) must be reported by the Investigators to Italfarmaco S.p.A. within 24 hours of learning of its occurrence.
Related SAEs MUST be collected and reported even if the study has been closed.
The Investigator must notify the SAE to the ~~Italfarmaco S.p.A.~~ Drug Safety Unit (**hereinafter "**DSU**")** **of Italfarmaco S.p.A.** by **sending**~~faxing~~ the SAE ~~f~~**F**orm, **according with the procedures described in the study manual and** within 24 hours of **learning of its occurrence**.
The details of the DSU are specified below:~~a SAE, at the number specified below; then, the Investigator must confirm any SAE notifications by mailing to the mail address or phoning to the phone number specified below:~~

Italfarmaco S.p.A.
PPD
Drug Safety Unit
~~Italfarmaco S.p.A.~~
Via dei Lavoratori, 54
20092 Cinisello Balsamo (MI), Italy
Phone: PPD
Fax: PPD
Fax (back-up): PPD
~~m~~**M**obile: PPD
e-mail: PPD
~~mobile~~ PPD

GLOSSARY OF ABBREVIATIONS

…

CRF	Case Report Form
CRO	Contract Research Organization
CMO	**Contact Manufacturing Organization**
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for AE
DSU	Drug Safety Unit

…

STUDY SYNOPSIS

STUDY TITLE	A two-part study to assess the safety and preliminary efficacy of Givinostat in patients with $JAK2^{V617F}$ positive Polycythemia Vera.
STUDY NUMBER	DSC/12/2357/45
EUDRACT No.	2013-000860-27
STUDY TYPE	International
CLINICAL PHASE	Ib/II
DISEASE	Patients with JAK2 positive chronic myeloproliferative neoplasms (cMPN), particularly Polycythemia Vera (PV).
STUDY RATIONALE	In recent years several reports have documented that histone deacetylases (HDACs) inhibitors induce neoplastic cells to undergo growth arrest, differentiation and/or apoptotic cell death. Among these agents, Givinostat (ITF2357) has most recently demonstrated effects on haematological parameters as well as constitutional parameters in patients with 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 can be expected with increased

	doses of Givinostat. Since the MTD of Givinostat has not been defined previously, the first aim of the current study is, therefore, to determine the maximum tolerated dose 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 Maximum Tolerated Dose (MTD) of Givinostat. The second aim of this study is to characterize the clinical efficacy of Givinostat at the MTD.
PRIMARY OBJECTIVES	*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. • To determine the safety and tolerability of Givinostat at the MTD *after 3 cycles*.
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. • 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. • To determine the safety and tolerability of Givinostat at the MTD *after 6 cycles*. • To characterize PK.
EXPLORATORY OBJECTIVES	*Parts A* and *B* • To evaluate the effect of Givinostat on single parameters of the clinico-haematological ELN response criteria. • 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 the "new" ELN response criteria (i.e. the revised ELN response criteria).
PRIMARY ENDPOINTS	*Part A* • Safety and tolerability evaluated as following: - 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). • Determination of the MTD of Givinostat based on cycle 1 DLT's. *Part B* • Overall response rate - i.e. Complete Response (CR) and Partial Response (PR) - of Givinostat at the MTD *after 3 cycles*; the response will be evaluated according to the clinico-haematological ELN response criteria. • Safety and tolerability of Givinostat at the MTD *after 3 cycles* evaluated as following: - Number of patients experiencing adverse events; - Type, incidence, and severity of treatment-related adverse events, graded according to CTCAE v. 4.03.
SECONDARY ENDPOINTS	*Part A* • Overall response rate - i.e. Complete Response (CR) and Partial Response (PR) - of Givinostat at the MTD *after 3 and 6 cycles*; the response will be evaluated according to the clinico-haematological ELN response criteria.

	• Individual Givinostat concentrations tabulated by dose cohort along with descriptive statistics. *Part B* • Overall response rate - i.e. Complete Response (CR) and Partial Response (PR) - of Givinostat at the MTD *after 6 cycles*; the response will be evaluated according to the clinico-haematological ELN response criteria. • Safety and tolerability of Givinostat at the MTD *after 6 cycles* evaluated as following: - Number of patients experiencing adverse events; - Type, incidence, and severity of treatment-related adverse events, graded according to CTCAE v. 4.03. • Individual Givinostat concentrations tabulated with descriptive statistics.
EXPLORATORY ENDPOINTS	*Part A* and *Part B* • To evaluate the effect of Givinostat on each single response parameter according to the clinico-haematological ELN response criteria. • To evaluate the effects of Givinostat on PD markers by mRNA analysis. • To evaluate the effects of Givinostat on spleen size (by MRI or CT scan) in patients with confirmed splenomegaly at baseline. • Improvement of constitutional symptoms evaluated according to MPN-SAF QOL questionnaire. • Reduction of the $JAK2^{V617F}$ allele burden, tested by quantitative RT-PCR. • Reduction of the symptomatic treatment of pruritus in term of dosage and/or days of treatment. *Part B* • Overall response rate - i.e. Complete Remission and Partial Remission - of Givinostat at the MTD *after 6 cycles*; the response will be evaluated according to the "new" ELN response criteria (i.e. the revised ELN response criteria). • To evaluate the effect of Givinostat on each single response parameter according to the "new" ELN response criteria (i.e. the revised ELN response criteria).

STUDY DESIGN	Two-part, multicenter, open label, non-randomized, phase Ib/II study.
NUMBER OF PATIENTS	About 52 evaluable patients, approximately 24 in *Part A* and 28 in *Part B*.
TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION	Givinostat is a histone-deacetylases inhibitor. The product will be supplied as hard gelatine capsules for oral administration at the strength of 50 mg **and/or 75 mg** and/or 100 mg each. In *Part A* patients will treated in Dose Levels (DLs) at the following 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, additionally DLs may be used to establish the MTD. In *Part B* patients will be treated at the MTD established in *Part A*.
TREATMENT PLAN	This is a two-part, multicenter, 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 finding part while *Part B* is assessing the preliminary efficacy. Patients will be enrolled either in *Part A* or *Part B* and transition from one part to the other is not allowed. Eligible patients for this study will have a confirmed diagnosis of PV according to the revised WHO criteria and the $JAK2^{V617}$ 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 may be expanded to all patients with cMPN. Study therapy will be administered in 28 day cycles (4 weeks of treatment). Disease response will be evaluated according to the ELN criteria 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 will not be 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 will be allowed to continue treatment with Givinostat (at the same dose and schedule) in a long-term study (Study N.: DSC/11/2357/44), **provided that the long-term study has already received all necessary approvals in that specific country and site, and the study has been already initiated in that particular site**. Safety will be monitored at each visit throughout the entire duration of the study. Treatment will be administered on an outpatient basis and patients will be followed regularly with physical and laboratory tests, as specified in the protocol; in case of hospitalization, the treatment will be continued or interrupted according to the Investigators' decision. *Part A* *Part A* is the dose escalation part of this study, evaluating the safety and tolerability and MTD of Givinostat in patients with $JAK2^{V617F}$ positive PV. Approximately 24 patients will be enrolled in this part of the study. In *Part A*, Dose Limiting Toxicity (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 will be graded according to CTCAE v. 4.03. Dose escalation will be conducted according to a standard 3+3 design, adopting a modified Fibonacci escalation schema. Patients will be enrolled in cohorts of 3 new patients (up to a maximum of 6) in rising dose levels.

Givinostat daily dose	Givinostat dose level (DL)	DL used primarily to asses
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.) has been previously shown to be well tolerated in several disorders and also in cMPN patients (Study N. DSC/07/2357/28 and Study N. DSC/08/2357/38). 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, additionally DLs may be introduced to more accurately define the MTD.

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) have been treated for 1 cycle, tolerability data will be evaluated and a decision to escalate to the next dose will be made.

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

At any time, if ≥ 2/3 or ≥ 2/6 patients at a given dose level develop a DLT, it is acceptable to de-escalate to an intermediate, not previously studied dose, 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 will start at the next lower dose below where ≥ 2/3 or ≥ 2/6 DLTs were observed (i.e. the MTD dose level).

If 2 or more patients per dose level experience a DLT, dose escalation will terminate and the MTD is the next lower dose level if no more than one out of 6 patients had a DLT at that level. Once all patients

	enrolled in *Part A* have been treated for at least 1 cycle, the study team will 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 will be permitted prior to determining the MTD. At that time, ~~continuing~~ patients **on treatment** at lower dose levels may be allowed to escalate their Givinostat dose **up** to the MTD the remainder of the study (*Part* ~~*AB*~~) at the discretion of the Investigator and ~~Sponsor~~ **after the written authorization of Italfarmaco S.p.A.**. **Of note, patients initially dosed at lower dose levels that are allowed to escalate their Givinostat dose up to the MTD for the remainder part of the study (*Part A*), will follow the dose modification rules of *Part B*.** Only PV patients from *Part A* assigned to the dose selected for *Part B* (MTD) may be counted towards the efficacy assessment in *Part B*. *Part B* *Part B* is a multicenter, 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. Approximately twenty eight patients will be enrolled in *Part B* at the MTD defined in *Part A*, according to an optimized Simon's 2-stage design. The dose of Givinostat will be modified for protocol specified toxicities. ~~Patients experiencing severe toxicity will have their treatment interrupted until recovery of the toxicity and then restarted at a reduced dose level. After the second occurrence of dose limiting toxicity patients will be permanently withdrawn from the study.~~
INCLUSION CRITERIA	1. Patients must be able to provide informed consent and be willing to sign an informed consent form; 2. Patients must have an age ≥18 years; 3. Patients must have a confirmed diagnosis of PV according to the revised WHO criteria; 4. Patients must have $JAK2^{V617F}$ positive disease; 5. Patients must have an active/not controlled disease defined as a) HCT ≥ 45% *or* HCT <45% in need of phlebotomy, and b) PLT counts > 400 $x10^9$/L, and

	c) WBC > 10 x10^9/L; 6. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 in *Part A*, ECOG performance status ≤ 2 in *Part B* within 7 days of initiating study drug; 7. Female patient of childbearing potential has a negative serum or urine pregnancy test within 72 hours of the first dose of study therapy; please note that a borderline urine pregnancy test must be followed with a serum pregnancy test; 8. Use of an effective means of contraception for women of childbearing potential and men with partners of childbearing potential; 9. Adequate and acceptable organ function within 7 days of initiating study drug; 10. Willingness and capability to comply with the requirements of the study. Note that if the enrolment in *Part A* is slow (i.e. < 5 patients enrolled in 3 months), eligibility for this part of the study may be expanded to all patients with cMPN. In this case, the inclusion criteri~~a~~**on n. 5** will be modified as following only for *Part A*: 5. Patients must have an active/not controlled disease defined as: a) *ET patients:* PLT counts > 600 x10^9/L; b) *MF patients:* no response according to EUMNET criteria. Note that an *effective* means of contraception for women of childbearing potential and men with partners of childbearing potential (i.e. inclusion criteri~~a~~**on n.** 5) is defined as following described based on different subject subgroups: **A.** *Female subjects of childbearing potential:* acceptable non-hormonal, contraceptive methods must be used from the 28 days before first dose of study drug through 3 months after the last dose of study drug and include the following: • True abstinence (absence of any sexual intercourse), when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. • Double barrier contraception such as diaphragm or a barrier

	method of contraception in conjunction with spermicidal jelly such as for example cervical cap with spermicide jelly and the male partner must use a condom with spermicide. • 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 a negative sperm post-vasectomy semen analysis) at least 6 months previously and 1 additional acceptable contraception method. **B.** *Female subjects of non-childbearing potential* must meet at least 1 of the following criteria: • Postmenopausal: Female subjects, less than 60 years of age, who have been amenorrheic for at least 2 years and have a serum FSH level within the laboratory's reference range for postmenopausal females. Female subject who are 60 years of age or older who are amenorrheic for greater than 2 years will be assume to be postmenopausal. • Documented hysterectomy or bilateral oophorectomy or both **a**~~A~~ll other female subjects (including subjects with tubal ligations and subjects that do not have a documented hysterectomy) will be considered to be of childbearing potential. **C.** *Male Subjects*, acceptable contraceptive methods must be used from Screening Visit through 3 months after the last dose of study drug, and include the following: • True abstinence (absence of any sexual intercourse), when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. • Condom with spermicide and the female partner must use an acceptable method of contraception, such as an oral, transdermal, injectable or implanted steroid-based contraceptive, or a diaphragm or a barrier method of contraception in conjunction with spermicidal jelly such as for example cervical cap with spermicide jelly. • Vasectomy (with a negative sperm post-vasectomy semen

	analysis) at least 6 months previously and 1 additional acceptable contraception method. • Male subjects must not donate sperm from the Screening Visit through 3 months after the last dose of study drug. Note also that – Male condom cannot be used with female condom due to risk of tearing. – The use of birth-control methods does not apply if the female partner has a bilateral oophorectomy, hysterectomy, or is postmenopausal (as defined above).
EXCLUSION CRITERIA	1. Active bacterial or mycotic infection requiring antimicrobial treatment; 2. Pregnancy or nursing; 3. A clinically significant QTc prolongation at baseline (e.g. repeated demonstration of a QTc interval ≥ 450 msec); 4. Use of concomitant medications known to prolong the QT/QTc interval; 5. Clinically significant cardiovascular disease including: a) Uncontrolled hypertension despite medical treatment, myocardial infarction, unstable angina within 6 months from study start; b) New York Heart Association (NYHA) Grade II or greater congestive heart failure; c) History of any cardiac arrhythmia requiring medication (irrespective of its severity); d) A history of additional risk factors for TdP (e.g. heart failure, hypokalemia, family history of Long QT Syndrome); 6. Known positivity for HIV; 7. Known active HBV and/or HCV infection; 8. Platelet count < 100 x 10^9/L within 14 days before enrolment (i.e. the receipt of the Patient ID); 9. Absolute neutrophil count < 1.2 x 10^9/L within 14 days before enrolment (i.e. the receipt of the Patient ID); 10. Serum creatinine > 2 x ULN; 11. Total serum bilirubin > 1.5 x ULN except in case of Gilbert's disease; 12. Serum aspartate aminotransferase/alanine aminotransferase (AST/ALT) > 3 x ULN;

	13. History of other diseases (including active tumours), metabolic dysfunctions, physical examination findings, or clinical laboratory findings giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk from treatment complications; 14. Prior treatment with a JAK2 or HDAC inhibitor or participation in an interventional clinical trial for cMPN, including PV, ET or MF; 15. Systemic treatment for cMPN other than aspirin/cardio aspirin; 16. Hydroxyurea within 28 days before enrolment (i.e. the receipt of the Patient ID); 17. Interferon alpha within 14 days before enrolment (i.e. the receipt of the Patient ID); 18. Anagrelide within 7 days before enrolment (i.e. the receipt of the Patient ID); 19. Any other investigational drug or device within 28 days before enrolment (i.e. the receipt of the Patient ID); 20. Patient with known hypersensitivity to the components of study therapy. **Of note, a *repeated* demonstration of a QTc interval ≥ 450 msec (i.e. exclusion criterion n. 3) means that, if the first ECG evaluation demonstrates 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) must be performed. The averaged value of these three ECG evaluations has to be used for the evaluation of the QTc interval requested by the exclusion criterion n. 3. In the CRF all the performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*.** **Note that an *any other investigational drug or device* (i.e. exclusion criterion n. 19) includes any investigational drug or device not already mentioned and detailed in the exclusion criteria n. 14, 15, 16 17 and/or 18.**
DURATION OF TREATMENT	The study (both *Part A* and *Part B*) will last up to a maximum of 24 weeks of treatment. However, after completion of the trial, all patients achieving clinical

	benefit will be allowed to continue treatment with Givinostat (at the same dose and schedule) in a long-term study (Study N.: DSC/11/2357/44), **provided that the long-term study has already received all necessary approvals in that specific country and site, and the study has been already initiated in that particular site**.
CONCOMITANT TREATMENT	Patients must NOT receive the following treatments during the study: a) Other investigational drugs while on this study; b) Cytotoxic agents, interferons or other approved treatment for cMPN other than aspirin/cardio-aspirin; c) Any drug known to provoke TdP. Other concomitant medications (e.g. symptomatic treatment of pruritus) and significant non-drug therapy (e.g. phlebotomy, blood transfusion) are permitted.
CRITERIA FOR RESPONSE	*Criteria for assessing clinico-haematological improvement* Disease response will be evaluated according to the following clinico-haematological ELN criteria *after 3 and 6 cycles* of treatment with Givinostat both in *Part A* (secondary endpoints) and in *Part B* (primary and secondary endpoints, respectively). • *Complete response*: 1. HCT<45% without phlebotomy, and 2. platelets ≤ 400 x10^9/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. As an exploratory endpoint, disease response will be 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*. • *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 hemorrhagic 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 hemorrhagic 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. the revised ELN response criteria): 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. Only in case the enrolment in *Part A* is slow (i.e. < 5 patients enrolled in 3 months) and the eligibility <u>for this part of the study</u> may be expanded to all patients with cMPN, disease response <u>for this part of the study</u> will be evaluated according to the ELN and EUMNET criteria after 3 and 6 cycles of treatment with Givinostat, in ET and MF patients, respectively. For ET (from the clinico-hematological ELN response criteria): • *Complete response:* 1. platelets ≤ 400 x10^9/L, <u>and</u> 2. no disease related systemic symptoms (i.e. pruritus, headache, microvascular disturbances), <u>and</u> 3. normal spleen size, <u>and</u> 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, <u>or</u> 2. Platelet count decrease > 50% from baseline. • *No response*: any response that does not satisfy partial response. In all cases, both for PV and ET patients, all phlebotomies performed in the first 3 weeks of treatment will <u>not</u> be 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. <u>*Complete response in anaemia*</u>*:* 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. <u>*Complete response in splenomegaly*</u>*:* Spleen not palpable; 3. <u>*Complete response in constitutional symptoms*</u>*:* 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 anaemia*: Increase of Hb ≥ 2 g/dL (but Hb < 12 g/dL) for non-RBC transfusion –dependent patients; or reduction ≥ 50% of transfusion requirement for RBC transfusion-dependent patients. 2. *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. 3. *Partial response in platelet count:* A ≥ 50% decrease in platelet count if baseline > 800 x10^9/L or platelet count increase by ≥ 50% x 10^9/L if baseline < 100 x10^9/L. 4. *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 5. *Progression in anaemia:* A hemoglobin decrease of ≥ 2 g/dL or a 50% increase in transfusion requirement or becoming transfusion dependent 6. *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. 7. *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- <u>or</u> platelet-based response without progression in anaemia, splenomegaly, <u>or</u> 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 will be evaluated directly by patients according to MPN-SAF QOL questionnaire. *Criteria for determination of MTD* Once all patients enrolled in *Part A* have been treated for at least 1 cycle, the study team will 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 will be permitted prior to determining the MTD.** **At that time, patients on treatment at lower dose levels may 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 <u>and</u> after the written authorization of Italfarmaco S.p.A.. Of note, patients initially dosed at lower dose levels that are allowed to escalate their Givinostat dose up to the MTD for the remainder part of the study (*Part A*), will follow the dose modification rules of *Part B*.** *Criteria for characterization of PK* Plasma concentrations from *Parts A* and *B* will be evaluated by dose and time point for all patients and time points with at least 1 PK assessment.
DOSE MODIFICATIONS RULES**, TREATMENT INTERRUPTION AND TREATMENT DISCONTINUATION**	**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.** **Dose modification criteria in *Part A*** **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. The first dose modification should be one dose level below the current**

	dose, the second modification should be two dose levels below. Study drug may be resumed at lower dose level once the event resolves to at least grade 1 or baseline values. If toxicities meeting modification criteria occur after the second dose reduction, therapy must be discontinued. **Patients with unresolved toxicities lasting 2 weeks or longer will not be permitted to continue on study.** **Patients experiencing Grade 3 or 4 unmanageable toxicity will require immediate dose interruption and notification to the Sponsor. Treatment for each new cycle will be delayed until dose limiting toxicities that are clearly not related to disease progression have resolved to at least Grade 1 or the patient's baseline.** **Dose modification criteria in *Part B*** **Dose adjustments are permitted for patients who do not tolerate the protocol-specified dosing schedule, in order to allow to these patients to continue the treatment with Givinostat. 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.** **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).** **Each dose modification has to be recorded on the CRF.** **Patients initially dosed at lower dose levels in *Part A* that, after the definition of MTD, are 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 written authorization of Italfarmaco S.p.A., will follow the dose modifications criteria for *Part B*.** **Total daily dose may never exceed the MTD defined in *Part A* (i.e. 100 mg b.i.d.).** **Treatment interruption and treatment discontinuation in *Parts A* and *B*** **In some circumstances, it may be necessary to temporarily**

	interrupt treatment as a result of adverse experiences that may have an unclear relationship to study drug. Study drug may be withheld by the Investigator at any time if there is concern about patient safety and for all aspects of the conduct of the protocol, since the safety of the individual patient is paramount. Treating Investigator may employ any means necessary to ensure patient safety, particularly in medical circumstances not anticipated by this protocol. **Dose adjustments are permitted for patients who do not tolerate the protocol-specified dosing schedule, in order to allow to these patients to continue the treatment with Givinostat. The objective of the Givinostat dose adjustment rules is to optimize the response for each individual patient, avoiding specific drug-related toxicities.** **If the patient inadvertently misses a drug dose, no additional trial medication should be taken that day or in the next days in the effort to replace the material that has been missed.** **If vomiting occurs, no additional trial medication should be taken that day in an effort to replace the material that has been vomited.** **If the study drug is interrupted for any reason for more than 4 weeks continuously, dosing may be not be restarted.** **Patients have the right to withdraw from the study at any time for any reason. The Investigator has the right to withdraw patients from the study due to medical reasons according to his/her discretion.** **If a pregnancy occurs, the patient will be replaced and another patient in that DL should be recruited.** **If the patient discontinues the study because of an adverse event whether or not drug related, he/she must be followed until resolution or stabilization of the event, whichever occurs first.** **In case of lack of compliance or in case the patient is found not eligible, the patient discontinuation have to be discussed between Investigator and Sponsor.** **If the patient discontinues for any reason (including discontinuation for pregnancy), with drug related adverse event ongoing at study end, he/she must be followed until resolution or stabilization of the event or until it is reasonable to consider the event not drug related any more or until the start of a new treatment, whichever occurs first.** **If the patient needs to take one of the concomitant medications included in list of "Drugs with risk of Torsades de Pointes", the treatment with Givinostat is to be promptly discontinued and the**

	patient must leave the study. **In case of multiple reasons (e.g. patient withdraws the consent for toxicity), "adverse events" should be indicated as the primary reason whenever applicable. All relevant information related to the reason for treatment discontinuation including contributory factors must be included on the 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. Should any drug-related AE still be ongoing beyond the last scheduled visit, this must be followed at subsequent follow-up visits until recovery. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance every effort should 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 must be included on the CRF.** ~~Patients have the right to withdraw from the study at any time for any reason. The Investigator has the right to withdraw patients from the study due to medical reasons according to his/her discretion.~~ ~~Patients experiencing Grade 3 or 4 unmanageable toxicity will require immediate dose interruption and notification of the Sponsor. Treatment for each new cycle will be delayed until dose limiting toxicities that are clearly not related to disease progression have resolved to at least Grade 1 or the patient's baseline.~~ ~~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. The first dose modification should be one dose level below the current dose, the second modification should be two dose levels below. Study drug may be resumed at lower dose level once the event resolves to at least grade 1 or baseline values. Patients with unresolved toxicities lasting 2 weeks or longer will not be permitted to continue on study.~~ ~~Patients enrolled in Part B of the study may have up to two dose modifications for DLT's or other drug related toxicities which interfere in the opinion of the investigator with continued safe and tolerable administration of therapy.~~ ~~If toxicities meeting modification criteria occur after the second dose reduction, therapy must be discontinued.~~ ~~Note that if a pregnancy occurs, the patient will be replaced and another patient in that DL should be recruited.~~ ~~Criteria for temporarily discontinuation~~

	~~Study drug should be temporarily stopped in Cycles 2 and beyond of Part A of and in all Part B for any drug related grade 2 toxicity, despite adequate supportive care (where applicable).~~ ~~In such cases, the following apply:~~ ~~treatment with Givinostat must be promptly discontinued and the patient remains untreated until recovery of the observed toxicities to the level identified, as mandatory for treatment continuation;~~ ~~in any event if recovery from previous toxicities takes 4 weeks or more, the experimental treatment shall not be restarted and the patient must discontinue the study.~~ ~~Note that these temporary stopping rules will be applied only to drug-related AE's.~~ ~~If vomiting occurs, no additional trial medication should be taken that day in an effort to replace the material that has been vomited.~~ ~~If the patient inadvertently misses a drug dose, no additional trial medication should be taken that day or in the next days in the effort to replace the material that has been missed.~~
STATISTICAL METHODS	This is a two-part, multicenter, open label, non-randomized, phase Ib/II study. A standard 3+3 design adopting a modified Fibonacci escalation schema will be used in *Part A*. Sample size for *Part B* was discussed for the primary endpoint defined as the Overall Response Rate after 3 cycles. A Simon's 2-stage design will be employed enrolling up to 28 patients in *Part B* with the aim of testing the "null hypothesis" that RR $\leq$ 0.50 versus the "alternative" that RR $\geq$ 0.75. Response rate will be assessed as defined in the Criteria for Response section. Overall up to 28 patients will need to be recruited, 12 patients being enrolled in Stage-1. Futility will be assessed after 12 patients enrolled (Stage 1). Please note that PV patients enrolled at the MTD in *Part A* may be counted towards Stage 1. Under the "null hypothesis" (if RR = 0.50), the expected total sample size is of 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 favour 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 respond to the treatment the trial will be terminated rejecting the "alternative" that RR $\geq$ 0.75. Otherwise, the trial goes on to Stage-2 enrolling further 16 patients to a total of 28 patients. If at the end of Stage-2, a total of 17 or fewer patients respond

	to the treatment the "alternative hypothesis" that RR $\geq$ 0.75 will be rejected; alternatively, if 18 or more patients respond, the "null hypothesis" that RR $\leq$ 0.50 will be rejected. Estimations are obtained from proprietary software (based on SAS ® 9.2) according to the algorithm proposed by R. Simon. Summary statistics will be calculated for all variables. For each continuous variable, the mean, standard deviation, median, minimum value and maximum value will be computed. For each discrete variable the number of patients in each category with non-missing values in relation to all patients with non-missing values of that variable will be provided. Results will be displayed within each cohort and overall, where applicable. Statistical calculations will be carried-out by resorting to SAS version 9.2 (or later). Both continuous and categorical data will be summarized and tabulated in 2-way tables (variable-by-visit). The main purpose of this phase Ib/II study consists in providing accurate estimates of clinically relevant variables and measures. From the statistical viewpoint this translates in estimating confidence intervals (CIs) with adequate precision where precision represents the degree of uncertainty. The two tailed 95% CIs of the sample estimates will be computed using parametric approaches if deemed appropriate. Otherwise the StatXact-4 software will be used in order to compute Exact/Nonparametric 95% CIs. Sub-groups analyses will be performed mainly for exploratory purposes. Since these analyses will be used to promote hypothesis 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. The following analysis sets will be defined: - Safety analysis set (SAF): The Safety analysis set will include all recruited patients who receive at least one dose of study medication. All safety analyses will be conducted on this population. - 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. **All efficacy analyses will be conducted on this population. All efficacy analyses will be**

	conducted on this population and they will be based on the *effective/actual* DL/daily doses of Givinostat at which each patient has been treated. - Per Protocol analysis set (PP): In order to assess the robustness of the efficacy analysis, the analysis of the efficacy endpoints could be repeated in 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. - MTD analysis set: The MTD analysis set will include all patients who experienced a DLT in Cycle 1 or received at least 90% of the doses of study medication in cycle 1. The first cycle data from this analysis set will be used to determine MTD. Patients who didn't experience a DLT and missed more than 10% of the doses in Cycle 1 of Part A will be replaced. - PK Analysis set: will consist of all SAF patients who with at least 1 PK assessment. This analysis set will be used for PK analysis. 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 **the** study. A listing of reasons of exclusion from analysis population will be provided. Italfarmaco S.p.A. will perform a preliminary analysis of data after the completion of **the first cycle of treatment from all patients recruited in** *Part A***, in order** to assess the MTD to be used for *Part B*. Moreover, a preliminary analysis will be performed on the 12 patients of the stage I (*Part B*). If six or fewer responses will be observed during the first stage then the study will be stopped. If seven or more responses will be observed in stage I, further 16 patients will be enrolled in *Part B*. In this case, a final statistical analysis will be performed considering all patients enrolled in the two study phases. In addition, Italfarmaco S.p.A. can perform a preliminary analysis of data in case of necessary safety and efficacy updates (e.g. to update regulatory documents and/or the drug safety profile, to revise the development program).

1.1 Medical indication and current treatments

Polycythemia Vera (PV), also termed Polycythemia rubra vera, together with Essential Thrombocythemia (ET) and Myelofibrosis (MF) belongs to a distinct group of Ph-chromosome-negative chronic myeloproliferative neoplasms (cMPN) characterized by clonal proliferation of multipotent haematopoietic stem cells leading to thrombocytosis, leukocytosis, erythrocytosis and bone marrow fibrosis [1, 2]. PV is characterized by a tri-lineage expansion of morphologically normal red cells, white cells, and platelets [3]. Generally, in PV it is possible to recognise two phases: (a) an initial proliferative polycythaemic phase, associated with increased red cell mass, which results in an increased propensity to thromboembolic events leading to significant morbidity and mortality, and (b) a "spent", or post-polycythaemic phase, in which cytopenias, including anaemia, are associated with ineffective haematopoiesis, bone marrow fibrosis and hypersplenism. The course of the disease is associated with a tendency to transform to myelofibrosis and leukaemia, events which may be influenced by treatment [4].
In 2005 the acquired mutation of the JAK2 kinase ($JAK2^{V617F}$) was discovered in PV patients [5, 6, 7, 8]. The JAK2 kinase, through its association with cytokine receptors and receptor tyrosine kinases, play a central role in cytokine signalling and signal transduction. The $JAK2^{V617F}$ mutation, that is present in about 90-95% of PV patients, results in expression of a constitutively activated JAK2 tyrosine kinase that confers growth factors independence and hypersensitivity to blood cell lines [5, 6, 8, 9].
PV is diagnosed in asymptomatic patients during the routine blood cell count analysis or, more commonly, on the basis of skin and mucous membrane redness or splenomegaly. Pruritus (aquagenic or not), fatigue, headache, vision disturbances, paraesthesia, erythromelalgia (acral dysesthesia and erythema) are the most common disease symptoms, that are present in the majority of patients and often severely deteriorate their quality of life [10, 11].
The long-term prognosis of PV patients is variable. Particularly without treatment, about half of the people who have PV with symptoms die in less than 2 years, while with treatment, median survival in PV is 15 years. The 10-year risk of developing either myelofibrosis (MF) or acute myeloid leukaemia (AML) is 10% and 6%, respectively. The primary causes of morbidity and mortality in PV patients are thrombosis, haematological transformation, and haemorrhage, responsible for 41%, 13% and 4% of deaths, respectively [12].
The first step in PV patient management is risk-stratification. The main two factors to be considered for risk-stratification are an age > 60 years and/or a history of thrombosis. Other factors, such as haematocrit, leukocytes and/or platelets counts and generic cardiovascular risk factors, are taken into account for risk stratification but their significance is still controversial.

In low risk patients, it is recommended to control the erythrocytosis by phlebotomy and, when no contraindication exists, to administer low-dose aspirin [2, 13]. In patients with intermediate risk of thrombosis, phlebotomy should be offered to keep the haematocrit below appropriate values and in general it is recommended to add a low daily dose of aspirin. When platelet counts are > 1000 x 109/L, additional myelosuppressive treatment should be considered. High-risk PV patients require cytoreductive therapy, even if the first step in the disease management is always phlebotomy plus low-dose aspirin [2].

Standard front-line therapy for high risk PV is hydroxycarbamide (formerly known as hydroxyurea, HU), the first choice cytoreductive agent [10, 13] authorised for PV therapy (both in Europe than in USA). Hydroxycarbamide is an antimetabolite that inhibits the enzyme ribonucleotide diphosphate reductase which has a rate-limiting role in DNA synthesis. It controls blood counts and reduces the rate of thromboembolic events. In general, hydroxycarbamide is well tolerated and has good clinical effect [4, 10], but its use is burdened by a not negligible rate of neoplastic transformation of the disease [14, 15].

In addition to hydroxycarbamide, PV patients can be also treated with alkylating agents (pipobroman and busulfan) authorised in Europe for treatment of PV. Pipobroman is a piperazine derivative and is available for clinical use in some European countries (France and Italy). The role of pipobroman in inducing the neoplastic transformation of PV has been recently emphasized as it appears to be even greater than that of hydroxycarbamide [14, 15]. Busulphan has been reported to be effective in controlling blood counts in PV since the 50's, but an extensive use of the drug is limited by its leukemogenic potential [4, 16]. In current clinical practice, pipobroman and busulfan are considered as second line therapies in hydroxycarbamide-intolerant or refractory cases [2].

Further to cytoreductive and anti-thrombotic therapy, very often patients are candidate to receive symptomatic treatments to control systemic symptoms, such as pruritus, headache, microvascular disturbances and fatigue, which can severely impair the patients' quality of life.

Recently, a JAK inhibitor was authorized both in Europe (i.e. Jakavi, INN: ruxolitinib) and in US (Jakafi, INN: ruxolitinib) for the treatment of adult patients with PV who are resistant to or intolerant of hydroxyurea.

The clinical course of PV and ET is marked by significant thrombotic complications and a variable risk to evolve into myelofibrosis and eventually to acute myeloid leukemia. Randomized clinical trials performed in USA and Europe have shown that cytoreductive treatment of blood hyperviscosity, chemotherapy and low-dose aspirin have dramatically reduced the number of thrombo-hemorrhagic episodes and substantially improved survival.

As compared to PV and ET, MF has the worst prognosis with a median survival or 3-5 years. A prognostic score system was developed where the presence of leukocytosis, leukopenia or anaemia was used to identify three groups of patients with different survival, from 1 to 8 years.

Conventional therapies in this disease were palliative and include many drugs in addition to supportive therapy to improve anaemia, thrombocytopenia and progressive splenomegaly.
Recently, a JAK inhibitor was authorized for the treatment of disease-related splenomegaly or symptoms in adult patients with MF in Europe (i.e. Jakavi, INN: ruxolitinib) and to treat intermediate or high-risk MF patient in US (i.e. Jakafi, INN: ruxolitinib).

1.2 Rationale

Polycythemia Vera (PV) is a myeloproliferative disorder which is considered to be a clonal disease derived from a transformed pluripotent hematopoietic stem cell. This cell is thought to lead to overactive hematopoiesis, driven by a constitutively active JAK-STAT signalling pathway, caused by V617F mutations within exons 12 and 14 of the JAK2 gene [17]. The clinical course of PV is marked by significant thrombotic complications with an estimated incidence of 18x1000 person-years, accounting for 45% of all deaths; myelofibrosis and transformation into AML may occur in a small percentage of cases (5x1000 person-years) [18].
The mainstay of current therapy is aimed at reducing the number of these disease related complications by reducing blood hyperviscosity. Cytoreductive agents have been proven efficacious in this regard, but concerns regarding acceleration of disease transformation remain, thereby substantiating the need for novel therapies [2].
Recently, small molecule inhibitors of the JAK2 kinase have at least partially validated the importance of this molecule in the clinical setting and several JAK2 inhibitors are currently under clinical development in PV. **Recently, a JAK inhibitor was authorized both in Europe (i.e. Jakavi, INN: ruxolitinib) and in US (Jakafi, INN: ruxolitinib) for the treatment of adult patients with PV who are resistant to or intolerant of hydroxyurea.**
Histone deacetylases (HDACs) are enzymes involved in the remodelling of chromatin and play a key role in the epigenetic regulation of gene expression.
Givinostat (ITF2357) is a potent, orally available small molecule inhibitor of HDACs and it has shown to interfere with the JAK/STAT signalling pathway in preclinical studies.

1.3 Preclinical rationale

Completed and updated data following described are reported in the Section 5 "Non-clinical studies" of the current Investigator Brochure Dossier related to ITF2357.
Givinostat has a**n anti-proliferative effect for tumor cells**~~broad antitumor activity on both solid and hematological tumors~~. **Its efficacy in hematological tumors bearing the JAK2V617F**

mutation is remarkable~~Amongst the latter, it has remarkable anti-proliferative activity against tumor cells bearing the JAK2^{V617F} mutation~~, showing an IC50 of 95 nM for SET-2 and 175 nM for HEL cell lines which are hetero- and homozygous for the mutant protein, respectively. These values are two- to three-fold lower than the ones observed for a JAK2 wild type tumor cell such as the erythroleukemic cell line K562, for which the IC50 is 350 nM [19, 20]. Combination benefit of Givinostat and hydroxyurea was observed in in-vitro cytotoxicity assays conducted in HEL and UKE cells.

1.4 Clinical studies

Completed and updated data following described are reported in the Section 6 "Effects in humans" of the current Investigator Brochure Dossier related to ITF2357.

Givinostat has been tested in a number of clinical studies. T**hree**~~wo~~ major indications have been explored with Givinostat, inflammatory disease**, neuromuscular disorders** and oncology. The most common AEs observed were thrombocytopenia as well as gastrointestinal toxicities. AEs were generally mild to moderate and reversible upon discontinuation of study drug. The maximum administered dose was a single dose of 600 mg in healthy volunteers and up to 400 mg once per week in patients with multiple myeloma. Doses up to approximately 100 mg b.i.d. were generally very well tolerated. At higher doses of Givinostat transient reduces haematological parameters (particularly platelets) and diarrhoea as well as nausea and vomiting were observed.

1.4.1 Givinostat in chronic myeloproliferative neoplasms

Givinostat is an HDACi and, as such, it has been investigated for its inhibitory activity on the autonomous proliferation of cells obtained by PV and ET patients carrying the JAK2^{V617F} mutation and to elucidate the mechanism of action of this inhibition. Cells obtained from PV or ET patients carrying the JAK2^{V617F} mutation are sensitive in colony assays to a 100-500 lower dose of Givinostat as compared to cells bearing un-mutated JAK2. Moreover, Givinostat promotes the outgrowth of normal colonies over that of JAK2^{V617F} mutated cells *in vitro* and induces down-modulation of the JAK2^{V617F} but not JAK2 wild type protein. JAK2^{V617F} inhibition by Givinostat takes place at the post-transcriptional level and is followed by down-modulation of the phosphorylated STAT5 protein and PRV-1 gene expression.

Two phase II study were conducted in patients with JAK2^{V617F} positive cMPN. A phase II of Givinostat monotherapy, was completed with positive results in patients with JAK2^{V617F} positive PV, ET and MF (Study N.: DSC/07/2357/28) [**22**]. Another phase II study combining Givinostat with hydroxyurea, was recently completed with positive results in patients with JAK2^{V617F} positive PV not responding to the maximum tolerated dose of hydroxyurea monotherapy (Study N. DSC/08/2357/38); a total of 44 PV patients received Givinostat doses of either 50 or 100 mg per day and were treated for up to 24 weeks [**23**]. The ELN response criteria [**21**] were used to assess the primary endpoint after 12 weeks of treatment. Complete or partial responses were observed in approximately 50% of patients across both dose levels.

At the time being, a multicenter, open label, long-term study testing the long term safety, tolerability and efficacy of Givinostat in patients with cMPN following core protocols and/or patient-named compassionate use program is ongoing (Study N. DSC/11/2357/44).

After completion of this current trial (Study N. DSC/12/2357/45), all patients achieving clinical benefit will be allowed to continue treatment with Givinostat (at the same dose and schedule) in the above mentioned long-term study (Study N.: DSC/11/2357/44)**, provided that the long-term study has already received all necessary approvals in that specific country and site and the study was initiated in that particular site**.

4.1 Overall study design

This is a two-part, multicenter, 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* will commence where the preliminary efficacy of Givinostat in PV patients will be established. Patients will be 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) may be counted towards the efficacy assessment in Part B.

Eligible patients for this study will 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 may 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 will be a combination of his/her site ID, study part ID and patient screening number, e.g. IT01-A01) will be assigned to each patient and it will identify the patient within his/her enrolment confirmation by Italfarmaco S.p.A. or its designee and never be reused in case of screening failure. After the enrolment confirmation and the assignation of the dose level before the first drug intake, a unique patient identification code (i.e. patient ID which will be a combination of patient screening number ID

and dose level ID, e.g. IT01-A01-DL1) will be assigned to each patient and it will identify the patient throughout his/her participation in the study and never be reused in case of premature drop-out.

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

Disease response will be evaluated according to the clinico-haematological ELN criteria [21] 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 will not be 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 will be allowed to continue treatment with Givinostat (at the same dose and schedule) in a long-term study (Study N.: DSC/11/2357/44)**, provided that the long-term study has already received all necessary approvals in that specific country and site, and the study has been already initiated in that particular site**.

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

4.1.1.2 Study team definition

The study team will include: selected Principal Investigator/s (i.e. Chairman and/or Principal Investigator/s who recruited the patients under discussion), the **CRO** Medical Monitor, Italfarmaco' Medical Expert/s, Italfarmaco' Clinical Scientist~~Project Manager~~ and any other additional personnel**,** *if necessary*.

4.1.1.5 Definition of MTD

If 2 or more patients per dose level experience a DLT, dose escalation will terminate and the MTD is the next lower dose level if no more than one out of 6 patients had a DLT at that level. Once all patients enrolled in *Part A* have been treated for at least 1 cycle, the study team will 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 will be permitted prior to determining the MTD.

At that time, ~~continuing~~ patients **on treatment** at lower dose levels may 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 written authorization of Italfarmaco S.p.A.**~~Sponsor~~. **Of note, patients initially dosed at lower dose levels that are allowed to escalate their Givinostat dose up to the MTD for the remainder part of the study (*Part A*), will follow the dose modification rules of Part B (see paragraph 4.3.3.2). Total daily dose may never exceed the MTD defined in Part A (i.e. 100 mg b.i.d.).**

4.1.2 Part B

Part B is a multicenter, 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.

Approximately twenty eight patients will be enrolled in Part B starting at the MTD defined in *Part A* **(i.e. 100 mg b.i.d.)**, according to an optimized Simon's 2-stage design [30].

The dose of Givinostat will be modified for protocol specified toxicities **(see paragraph 4.3.3.2)**. ~~Patients experiencing severe toxicity will have their treatment interrupted until recovery of the toxicity and then restarted at a reduced dose level (see and). After the second occurrence of dose limiting toxicity patients will be permanently withdrawn from the study.~~

4.2 Trial organization

The conduct of this study will be committed to a Contract Research Organization (CRO). In any case, Italfarmaco S.p.A. remains responsible for the development, writing and finalization of the study protocol, the investigational medicinal product (IMP) production and the Pharmacovigilance activities.

For all study activities, with the exception above mentioned, the designated CRO **or them delegates (e.g. a Contact Manufacturing Organization (CMO) delegated for the IMP secondary packaging and management) can** ~~will~~ apply internal standard operating procedures (SOPs).

Trial activities will be supervised by Italfarmaco S.p.A. through regular contacts with the staff of the designated CRO **or their delegates** and/or Investigators, as necessary.

4.3.1 Inclusion criteria

Patients must meet the following criteria to be eligible for study entry:

1. Patients must be able to provide informed consent through the signature of an informed consent form;
2. Patients must have an age ≥18 years;
3. Patients must have a confirmed diagnosis of PV according to the revised WHO criteria;
4. Patients must have $JAK2^{V617F}$ positive disease;
5. Patients must have an **active/not controlled disease** defined as
   a) HCT ≥ 45% ***or*** HCT <45% in need of phlebotomy, **and**
   b) PLT counts > 400 $x10^9$/L, **and**
   c) WBC > 10 $x10^9$/L;
6. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status [**28**] ≤ 1 in ***Part A***, ECOG performance status ≤ 2 in ***Part B***, within 7 days of initiating study drug;
7. Female patient of childbearing potential has a negative serum or urine pregnancy test within 72 hours of the first dose of study therapy; please note that a borderline urine pregnancy test must be followed with a serum pregnancy test;
8. Use of an ***effective*** means of contraception for women of childbearing potential and men with partners of childbearing potential;
9. Adequate and acceptable organ function within 7 days of initiating study drug;
10. Willingness and capability to comply with the requirements of the study.

Note that if the enrolment in *Part A* is slow (i.e. < 5 patients enrolled in 3 months), eligibility for this part of the study may be expanded to all patients with cMPN. In this case, the inclusion criteri~~a~~**on n.** 5 will be modified as following only for ***Part A***:

5. Patients must have an **active/not controlled disease** defined as:
   a) ***ET patients:*** PLT counts > 600 $x10^9$/L;
   b) ***MF patients:*** no response according to EUMNET criteria [**29**].

Note that an *effective* means of contraception for women of childbearing potential and men with partners of childbearing potential (i.e. inclusion criteri~~a~~**on n.** 5) is defined as following described based on different subject subgroups:

A. *Female subjects of childbearing potential:* acceptable non-hormonal, contraceptive methods must be used from the 28 days before first dose of study drug through 3 months after the last dose of study drug and include the following:

- True abstinence (absence of any sexual intercourse), when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
- Double barrier contraception such as diaphragm or a barrier method of contraception in conjunction with spermicidal jelly such as for example cervical cap with spermicide jelly and the male partner must use a condom with spermicide.
- 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 a negative sperm post-vasectomy semen analysis) at least 6 months previously and 1 additional acceptable contraception method.

B. *Female subjects of non-childbearing potential* must meet at least 1 of the following criteria:

- Postmenopausal: Female subjects, less than 60 years of age, who have been amenorrheic for at least 2 years and have a serum FSH level within the laboratory's reference range for postmenopausal females. Female subject who are 60 years of age or older who are amenorrheic for greater than 2 years will be assume to be postmenopausal.
- Documented hysterectomy or bilateral oophorectomy or both **a**~~A~~ll other female subjects (including subjects with tubal ligations and subjects that do not have a documented hysterectomy) will be considered to be of childbearing potential.

C. *Male Subjects*, acceptable contraceptive methods must be used from Screening Visit through 3 months after the last dose of study drug, and include the following:

- True abstinence (absence of any sexual intercourse), when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
- Condom with spermicide and the female partner must use an acceptable method of contraception, such as an oral, transdermal, injectable or implanted steroid-based contraceptive, or a diaphragm or a barrier method of contraception in conjunction with spermicidal jelly such as for example cervical cap with spermicide jelly.
- Vasectomy (with a negative sperm post-vasectomy semen analysis) at least 6 months previously and 1 additional acceptable contraception method.
- Male subjects must not donate sperm from the Screening Visit through 3 months after the last dose of study drug.

Note also that

- Male condom cannot be used with female condom due to risk of tearing.
- The use of birth-control methods does not apply if the female partner has a bilateral oophorectomy, hysterectomy, or is postmenopausal (as defined above).

4.3.2 Exclusion criteria

Patients must NOT meet any of the following criteria to be eligible for study entry:

1. Active bacterial or mycotic infection requiring antimicrobial treatment;
2. Pregnancy or nursing;
3. A clinically significant QTc prolongation at baseline (e.g. repeated demonstration of a QTc interval ≥ 450 msec);
4. Use of concomitant medications known to prolong the QT/QTc interval;
5. Clinically significant cardiovascular disease including:
   a) Uncontrolled hypertension despite medical treatment, myocardial infarction, unstable angina within 6 months from study start;
   b) New York Heart Association (NYHA) Grade II or greater congestive heart failure;
   c) History of any cardiac arrhythmia requiring medication (irrespective of its severity);
   d) A history of additional risk factors for TdP (e.g. heart failure, hypokalemia, family history of Long QT Syndrome);
6. Known positivity for HIV;
7. Known active HBV and/or HCV infection;
8. Platelet count < 100 $x10^9$/L within 14 days before enrolment (i.e. the receipt of the Patient ID);
9. Absolute neutrophil count < 1.2 $x10^9$/L within 14 days before enrolment (i.e. the receipt of the Patient ID);
10. Serum creatinine > 2 x ULN;
11. Total serum bilirubin > 1.5 x ULN except in case of Gilbert's disease;
12. Serum aspartate aminotransferase/alanine aminotransferase (AST/ALT) > 3 x ULN;
13. History of other diseases (including active tumours), metabolic dysfunctions, physical examination findings, or clinical laboratory findings giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk from treatment complications;

14. Prior treatment with a JAK2 or HDAC inhibitor or participation in an interventional clinical trial for cMPN, including PV, ET or MF;
15. Systemic treatment for cMPN other than aspirin/cardio aspirin;
16. Hydroxyurea within 28 days before enrolment (i.e. the receipt of the Patient ID);
17. Interferon alpha within 14 days before enrolment (i.e. the receipt of the Patient ID);
18. Anagrelide within 7 days before enrolment (i.e. the receipt of the Patient ID)
19. Any other investigational drug or device within 28 days before enrolment (i.e. the receipt of the Patient ID);
20. Patient with known hypersensitivity to the components of study therapy.

Of note, a *repeated* demonstration of a QTc interval ≥ 450 msec (i.e. exclusion criterion n. 3) means that, if the first ECG evaluation demonstrates 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) must be performed. The averaged value of these three ECG evaluations has to be used for the evaluation of the QTc interval requested by the exclusion criterion n. 3. In the CRF all the performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*.

Note that an *any other investigational drug or device* (i.e. exclusion criterion n. 19) includes any investigational drug or device not already mentioned and detailed in the exclusion criteria n. 14, 15, 16 17 and/or 18.

4.3.3 Criteria for dose modifications, treatment interruption and treatment discontinuation

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.

~~Patients have the right to withdraw from the study at any time for any reason. The Investigator has the right to withdraw patients from the study due to medical reasons according to his/her discretion. When patients discontinue study medication, the reason must be categorized in the case report form (CRF) as one of the following:~~

~~1. study completed;~~
~~2. adverse event(s);~~
~~3. disease progression;~~
~~4. protocol violation;~~
~~5. patient withdrew Informed Consent Form;~~
~~6. lost at follow-up (despite every effort made to contact the patient);~~
~~7. physician decision due to safety reasons;~~

8. sponsor decision (see paragraph 8.7);
9. lack of compliance;
10. patient found not eligible;
11. death;
12. pregnancy.

If the patient discontinues the study because of an adverse event whether or not drug related, he/she must be followed until resolution or stabilization of the event, whichever occurs first.

In case of lack of compliance or in case the patient is found not eligible, the patient discontinuation have to be discussed between Investigator and Sponsor.

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

If the patient needs to take one of the concomitant medications included in list of "Drugs with risk of Torsades de Pointes" (see Appendix C) the treatment with Givinostat is to be promptly discontinued and the patient must leave the study.

In case of multiple reasons (e.g. patient withdraws the consent for toxicity), "adverse events" should be indicated as the primary reason whenever applicable. All relevant information related to the reason for treatment discontinuation including contributory factors must be included on the 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. Should any drug-related AE still be ongoing beyond the last scheduled visit, this must be followed at subsequent follow-up visits until recovery. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance every effort should 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 must be included on the CRF.

4.3.3.1 Dose modification criteria in *Part A*

Patients experiencing Grade 3 or 4 unmanageable toxicity will require immediate dose interruption and notification of the Sponsor. Treatment for each new cycle will be delayed until dose limiting toxicities that are clearly not related to disease progression have resolved to at least Grade 1 or the patient's baseline.

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 (see paragraph 4.1.1.1 for the DLT definition). The first dose modification should be one dose level below the current dose, the second modification should be two dose levels below. Study drug may be resumed at lower dose level once the event resolves to at least grade 1 or baseline values.

If toxicities meeting modification criteria occur after the second dose reduction, therapy must be discontinued. Figure 1 outlines the dose modifications scheme for all DLs of Givinostat monotherapy, with exception of DL0 (i.e. 50 b.i.d.) and DL1 (i.e. 100 mg b.i.d.) represented by Figures 2 and 3, respectively. Patients with unresolved toxicities lasting 2 weeks or longer will not be permitted to continue on study.

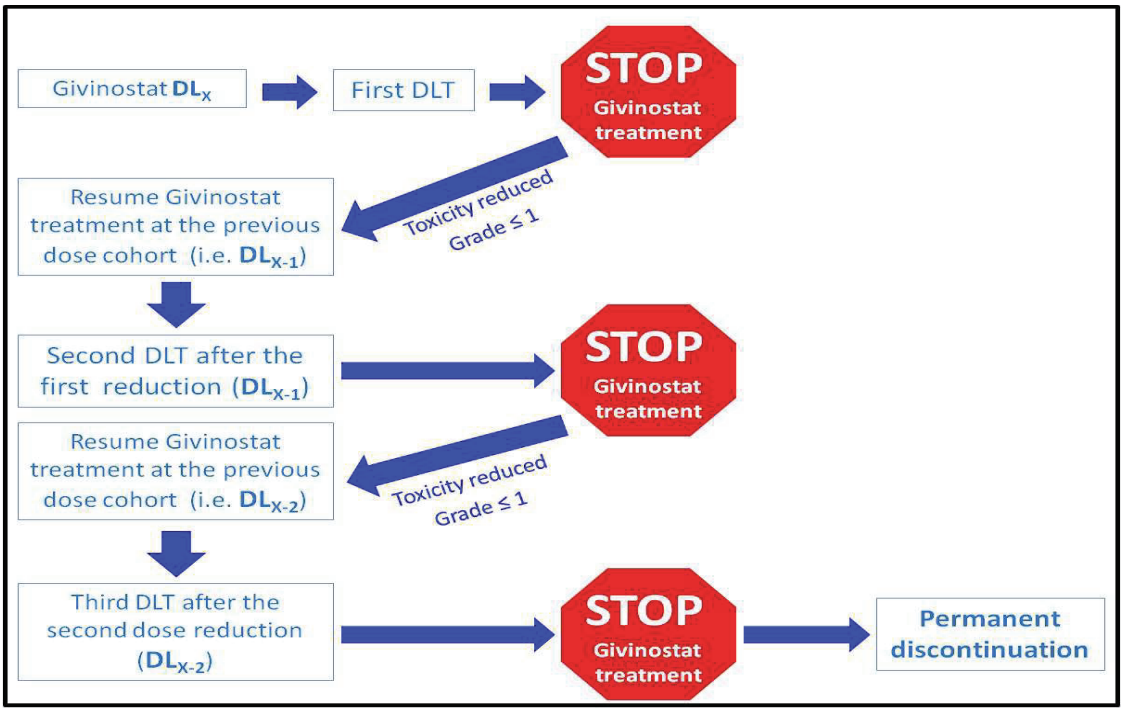
Patients experiencing Grade 3 or 4 unmanageable toxicity will require immediate dose interruption and notification of the Sponsor. Treatment for each new cycle will be delayed until dose limiting toxicities that are clearly not related to disease progression have resolved to at least Grade 1 or the patient's baseline.

~~Patients enrolled in Part B of the study may have up to two dose modifications for DLT's or other drug related toxicities which interfere in the opinion of the investigator with continued safe and tolerable administration of therapy.~~

~~If toxicities meeting modification criteria occur after the second dose reduction, therapy must be discontinued.~~

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

Figure 1 - Criteria for dose modifications



DLT is a Dose Limiting Toxicity. DL_x represents a Dose Level with the exception of DL0 (i.e. 50 mg b.i.d.) and DL1 (i.e. 100 mg b.i.d.), represented by Figures 2 and 3, respectively. DL_{x-1} represents the next lower Dose Level (first dose reduction). DL_{x-2} represents the next lower dose level after a first dose reduction (second dose reduction). Grade ≤ 1 represents the severity of AE.

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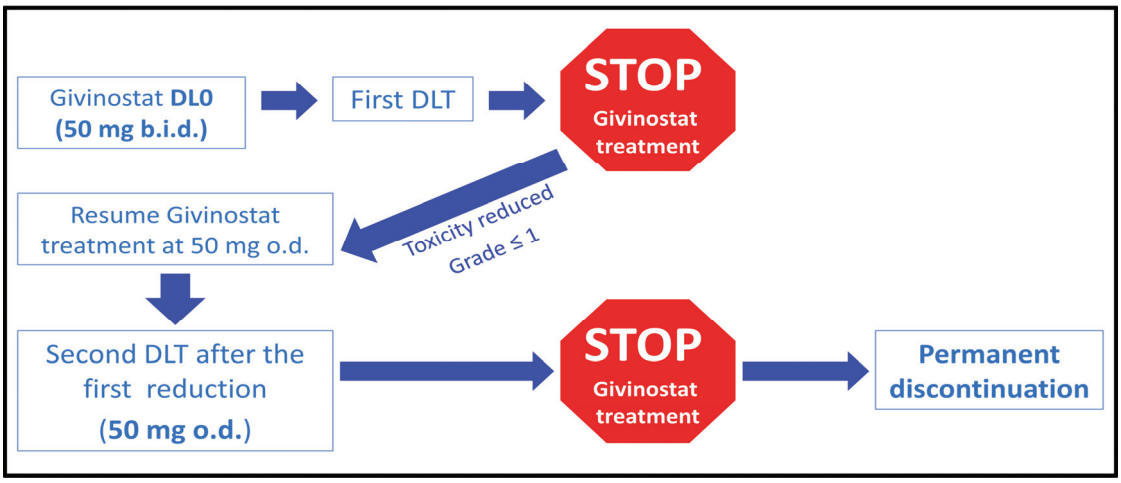
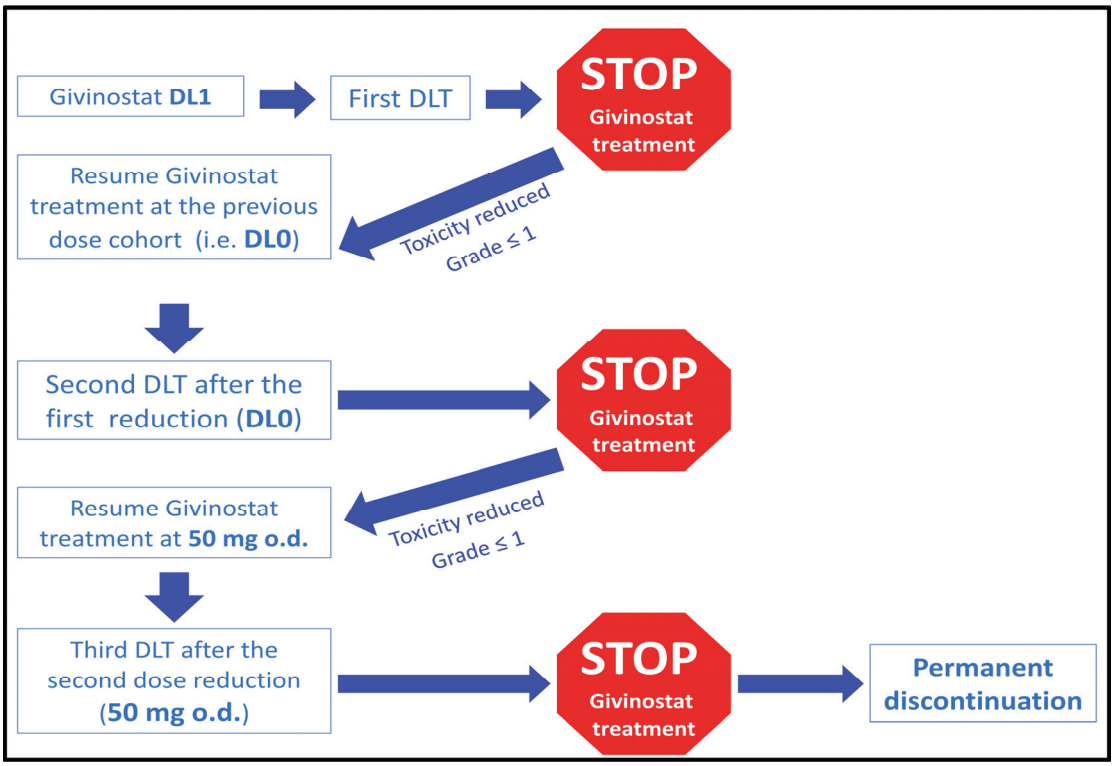
Figure 2 - Criteria for dose modifications for patients treated in DL0



DLT is a Dose Limiting Toxicity. Grade ≤ 1 represents the severity of AE.

Figure 3 - Criteria for dose modifications for patients treated in DL1



DLT is a Dose Limiting Toxicity. Grade ≤ 1 represents the severity of AE.

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4.3.3.1 Dose modification criteria in *Part B*

Dose adjustments are permitted for patients who do not tolerate the protocol-specified dosing schedule, in order to allow to these patients to continue the treatment with Givinostat. The guidelines described here below (i.e. see paragraph 3.3.3.2.1 and paragraph 3.3.3.2.2) need to be followed. The objective of the Givinostat dose adjustment rules described below 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 (see paragraph 3.3.3.2.1) 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 (see paragraph 3.3.3.2.2).
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).
Each dose modification has to be recorded on the CRF.
Of note, the dose modification criteria described in this paragraph (i.e. see paragraph 3.3.3.2.1 and paragraph 3.3.3.2.2 for details) will be followed also by patients initially dosed at lower dose levels in *Part A* that, after the definition of MTD, are allowed to escalate their Givinostat dose to the MTD for the remainder part of the study (*Part A*) at the discretion of the Investigator and after written authorization of Italfarmaco S.p.A..

4.3.3.1.1 Dose adjustments for safety reasons in *Part B*

In *Part B*, the initial dose of Givinostat will be the MTD defined in *Part A* (i.e. 100 mg b.i.d.).
Based on evaluations performed as part of the visit procedures of the Day 28 of each Cycle up to the Cycle 5 (i.e. Cycle 1 Day 28, Cycle 2 Day 28, Cycle 3 Day 28, Cycle 4 Day 28, Cycle 5 Day 28) and/or in any necessary additional study visit, the Givinostat doses have to be decreased in case of the occurrence of at least one of the toxicities described in the Table 3.
The objective of these guidelines is to consider the patient's data, prior clinic-haematological response and dose tolerability, in order to achieve an optimized dose for each individual patient, or a balancing between the tolerable dose and the clinico-haematological response, that also take into account the natural course of the disease.
Reductions in Givinostat total daily dose for patients that meet dose reduction criteria (see Table 3 for details) will be achieved by adjusting the morning and evening administered dose level, since the total daily dose is equally divided between the morning and evening administration.

Table 3 - Dose reduction rules in *Part B*

Observed values/data	Action
Grade 1 thrombocytopenia **(i.e. PLTs count < local LLN but ≥ 75 x 10^9/L)**	***Total daily dose must be reduced of 50 mg/die*:** • ***For patients that are receiving the daily dose of 100 mg b.i.d., daily dose must be reduced to 75 mg b.i.d..*** • ***For patients that are receiving a reduced daily dose of 75 mg b.i.d. or 50 mg b.i.d., daily dose must be evaluated* based on the Investigator's decision and after discussion with the Sponsor's representative(s).**
Grade 2 thrombocytopenia **(i.e. PLTs count < 75 x 10^9/L but ≥ 50 x 10^9/L)** ***or*** **Grade 2 anemia** **(i.e. Hb value < 10 g/dL but ≥ 8 g/dL)** ***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.**	***Total daily dose must be reduced of 50 or 100 mg/die, based on the Investigator's decision and after discussion with the Sponsor's representative(s):*** • ***For patients that are receiving the daily dose of 100 mg b.i.d.*, daily dose should be reduced to *75 mg b.i.d. or 50 mg b.i.d.*, based on the Investigator's decision and after discussion with the Sponsor's representative(s).** • ***For patients that are receiving a reduced daily dose of 75 mg b.i.d. or 50 mg b.i.d., daily dose must be evaluated* based on the Investigator's decision and after discussion with the Sponsor's representative(s).**
Grade 3 thrombocytopenia **(i.e. PLTs count < 50 x 10^9/L but ≥ 25 x 10^9/L)** ***or*** **Grade 3 anemia** **(i.e. Hb value < 8 g/dL; transfusion indicated)** ***or*** **Grade 3 febrile neutropenia** **(i.e. ANC < 1.0 x 10^9/L with a single temperature of > 38.3°C / 101° F, or a sustained temperature ≥ 38°C / 100.4°F for more than one hour)**	***Immediate temporary discontinuation of the treatment with Givinostat.*** **The treatment will be interrupted *for at least one week. Anyway*, the treatment for each new cycle will be delayed *until the observed toxicity* that is clearly not related to disease progression, *has resolved to at least Grade 1 or the patient's baseline value.*** **Daily dose has to be restarted at *75 mg b.i.d. or 50 mg b.i.d.*, based on the Investigator's**

	decision and after discussion with the Sponsor's representative(s). **Patients with unresolved toxicities lasting 4 weeks or longer will not be permitted to continue on study.**

Table 3 - Dose reduction rules in *Part B* (*continue*)

Observed values/data	Action
Grade 4 thrombocytopenia **(i.e. PLTs count ≤ 25 x 10^9/L)** ***or*** **Grade 4 anemia** **(i.e. life-threatening consequences; urgent intervention indicated)** ***or*** **Grade 4 febrile neutropenia** **(i.e. life-threatening consequences; urgent intervention indicated)** ***or*** **Grade ≥ 3 unmanageable toxicity**	***Immediate temporary discontinuation of the treatment with Givinostat.*** **The treatment will be interrupted *for at least one week*. *Anyway*, the treatment for each new cycle will be delayed *until the observed toxicity* that is clearly not related to disease progression, *has resolved to at least Grade 1 or the patient's baseline value.*** ***The continuation of the study - and the study drug dosage - should be evaluated based on the Investigator's decision and Sponsor's recommendation.*** **Patients with unresolved toxicities lasting 4 weeks or longer will not be permitted to continue on study.**

LLN is the Lower Limit of Normality of the value reported in each evaluation performed at local laboratory of each investigational site.

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).
Patients with unresolved toxicities lasting 4 weeks or longer will not be permitted to continue on study.
In order follow the evolution of the observed abnormalities up to its stabilization and/or normalization (i.e. event resolved to at least Grade 1 or baseline values) and also to provide sufficient data to make dose adjustment decisions, it is strictly recommended to perform additional study visits at least on bi-weekly basis upon occurrence of the following toxicities:

- **Grade 1 thrombocytopenia (i.e. PLTs count < local LLN but ≥ 75 x 10^9/L);**
- **Grade 1 anemia (i.e. Hb value < local LLN but ≥ 10 g/dL),**

- **ANC < 2.0 x 10^9/L;**
- **Grade 2 non-haematological toxicities;**
- **Any SAE (*if feasible*).**

In addition, additional study visits at least on weekly basis should be performed upon occurrence of the following toxicities:

- **Grade ≥ 2 thrombocytopenia (i.e. PLTs count < 75 x 10^9/L);**
- **Grade ≥ 2 anemia (i.e. Hb value < 10 g/dL),**
- **ANC ≤ 1.5 x 10^9/L;**
- **Drug-related Grade ≥ 3 non-haematological toxicities;**
- **Drug-related SAE (*if feasible*).**

Of note, the lowest dosage of Givinostat that can be dispensed to the patients in *Part B* is 50 mg b.i.d., i.e. a dosage that has been previously shown to be well tolerated. Of note, patients will self-administer daily Givinostat capsules at home at morning and at 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).

4.3.3.1.2 Dose increase for inadequate efficacy in *Part B*

In *Part B*, the initial dose of Givinostat will be the MTD defined in *Part A* (i.e. 100 mg b.i.d.).

Based on evaluations performed as part of the visit procedures of the Day 28 of each Cycle up to the Cycle 5 (i.e. Cycle 1 Day 28, Cycle 2 Day 28, Cycle 3 Day 28, Cycle 4 Day 28, Cycle 5 Day 28) and/or in any necessary additional study visit, the Givinostat doses have to be decreased in case of the occurrence specific toxicities (see paragraph 4.3.3.2.1).

After a dose reduction, dosing may be restarted and then increased following recovery of the observed toxicity(ies) to controlled levels. The objective for restarting and then escalating after a reduction for safety reasons is to find the highest safe dose regimen of Givinostat for each patient that is necessary to obtain a clinico-haematological response, with increase in dose not more than the MTD defined in *Part A* (i.e. 100 mg b.i.d.).

After a dose reduction and in order to optimize the response for each individual patient avoiding specific drug-related toxicities, the Givinostat dosage may be increased for patients who meet all the following criteria, based on evaluations performed as part of the visit procedures of the Day 28 of each Cycle up to the Cycle 5 (i.e. Cycle 1 Day 28, Cycle 2 Day 28, Cycle 3 Day 28, Cycle 4 Day 28, Cycle 5 Day 28):

1. **Inadequate efficacy as demonstrated by one or more of the following points:**
    a) **HCT ≥ 45%, *or* HCT < 45% but at least 1 phlebotomy performed after the first 3 weeks of treatment, *or* HCT < 45% but at least three point higher than the**

HCT obtained at baseline (i.e. HCT at baseline (in %) plus at least a value of 3%), *or*

b) **WBCs count > 10 x 10^9/L, *or***

c) **PLTs count > 400 x 10^9/L, and**

2. **PLTs count > local LLN, and**
3. **Hb value ≥ 12 g/dL, and**
4. **ANC ≥ 1.5 x 10^9/L.**

Table 4 summarizes the dose increase rules to be apply for Givinostat dosage at the end (i.e. Day 28) of each Cycle of *Part B* up to Cycle 5 (i.e. Cycle 1 Day 28, Cycle 2 Day 28, Cycle 3 Day 28, Cycle 4 Day 28, Cycle 5 Day 28). The objective of these guidelines is to consider the patient's data, prior clinico-haematological response and dose tolerability, in order to achieve an optimized dose for each individual patient, or a balancing between the tolerable dose and the clinico-haematological response, that also take into account the natural course of the disease.

Table 4 - Dose increase for inadequate efficacy in *Part B*

Observed values/data	Action
1. Inadequate efficacy as demonstrated by one or more of the following points: **d) HCT ≥ 45%, *or* HCT < 45% but at least 1 phlebotomy performed after the first 3 weeks of treatment, *or* HCT < 45% but at least three point higher than the HCT obtained at baseline (i.e. HCT at baseline (in %) plus at least a value of 3%), *or*** **e) WBCs count > 10 x 10^9/L, *or*** **f) PLTs count > 400 x 10^9/L, and** **2. PLTs count > local LLN, and** **3. Hb value ≥ 12 g/dL, and** **4. ANC ≥ 1.5 x 10^9/L.**	***Total daily dose may be increased of 50 mg/die:*** • ***For patients that are receiving a reduced daily dose of 75 mg b.i.d.*, daily dose must be increased to *100 mg b.i.d.*.** • ***For patients that are receiving a reduced daily dose of 50 mg b.i.d.*, daily dose must be increased to *75 mg b.i.d.*.** • ***Only for patients of Part A that are receiving a reduced daily dose of 50 mg o.d.*, daily dose must be increased to *50 mg b.i.d.*.**

The total daily dose increase may be no greater than an increase of 50 mg/die, since the following dose increase rules will apply as detailed in the Table 4:

- ***For patients that are receiving a reduced daily dose of 75 mg b.i.d.*, the dose increase criteria allow to receive a maximum dosage of 100 mg b.i.d.;**
- ***For patients that are receiving a reduced daily dose of 50 mg b.i.d.*, the dose increase criteria allow to receive a maximum dosage of 75 mg b.i.d..**
- ***Only for patients of Part A that are receiving a reduced daily dose of 50 mg o.d.*, the dose increase criteria allow to receive a maximum dosage of 50 mg b.i.d..**

Therefore, total daily dose may never exceed the MTD defined in *Part A* (i.e. 100 mg b.i.d.).

4.3.3.2 Treatment interruption and treatment discontinuation in *Parts A* and *B*

In some circumstances, it may be necessary to temporarily interrupt treatment as a result of adverse experiences that may have an unclear relationship to study drug. Study drug may be withheld by the Investigator at any time if there is concern about patient safety and for all aspects of the conduct of the protocol, since the safety of the individual patient is paramount. Treating Investigator may employ any means necessary to ensure patient safety, particularly in medical circumstances not anticipated by this protocol.
Dose adjustments are permitted for patients who do not tolerate the protocol-specified dosing schedule, in order to allow to these patients to continue the treatment with Givinostat (see paragraph 4.3.3.1 and paragraph 4.3.3.2). The objective of the Givinostat dose adjustment rules described below is to optimize the response for each individual patient, avoiding specific drug-related toxicities.
If the patient inadvertently misses a drug dose, no additional trial medication should be taken that day or in the next days in the effort to replace the material that has been missed.
If vomiting occurs, no additional trial medication should be taken that day in an effort to replace the material that has been vomited.
If the study drug is interrupted for any reason for more than 4 weeks continuously, dosing may be not be restarted.
Patients have the right to withdraw from the study at any time for any reason. The Investigator has the right to withdraw patients from the study due to medical reasons according to his/her discretion.
~~Note that these temporary stopping rules will be applied only to drug-related AE's.~~
~~If vomiting occurs, no additional trial medication should be taken that day in an effort to replace the material that has been vomited.~~
~~If the patient inadvertently misses a drug dose, no additional trial medication should be taken that day or in the next days in the effort to replace the material that has been missed.~~

When patients discontinue study medication, the reason must be categorized in the case report form (CRF) as one of the following:

1. **study completed;**
2. **adverse event(s);**
3. **disease progression;**
4. **protocol violation;**
5. **patient withdrew Informed Consent Form;**
6. **lost at follow-up (despite every effort made to contact the patient);**
7. **physician decision due to safety reasons;**
8. **sponsor decision (see paragraph 8.7);**
9. **lack of compliance;**
10. **patient found not eligible;**
11. **death;**
12. **pregnancy.**

If a pregnancy occurs, the patient will be replaced and another patient in that DL should be recruited.
If the patient discontinues the study because of an adverse event whether or not drug related, he/she must be followed until resolution or stabilization of the event, whichever occurs first.
In case of lack of compliance or in case the patient is found not eligible, the patient discontinuation have to be discussed between Investigator and Sponsor.
If the patient discontinues for any reason (including discontinuation for pregnancy), with drug related adverse event ongoing at study end, he/she must be followed until resolution or stabilization of the event or until it is reasonable to consider the event not drug related any more or until the start of a new treatment, whichever occurs first.
If the patient needs to take one of the concomitant medications included in list of "Drugs with risk of Torsades de Pointes" (see Appendix C) the treatment with Givinostat is to be promptly discontinued and the patient must leave the study.
In case of multiple reasons (e.g. patient withdraws the consent for toxicity), "adverse events" should be indicated as the primary reason whenever applicable. All relevant information related to the reason for treatment discontinuation including contributory factors must be included on the 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. Should any drug-related AE still be ongoing beyond the last scheduled visit, this must be followed at subsequent follow-up visits until recovery. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance every effort should 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 must be included on the CRF.

~~When patients discontinue study medication, the reason must be categorized in the case report form (CRF) as one of the following:~~

~~1. study completed;~~
~~2. adverse event(s);~~
~~3. disease progression;~~
~~4. protocol violation;~~
~~5. patient withdrew Informed Consent Form;~~
~~6. lost at follow-up (despite every effort made to contact the patient);~~
~~7. physician decision due to safety reasons;~~
~~8. sponsor decision (see paragraph 8.7);~~
~~9. lack of compliance;~~
~~10. patient found not eligible;~~
~~11. death;~~
~~12. pregnancy.~~

~~If the patient discontinues the study because of an adverse event whether or not drug related, he/she must be followed until resolution or stabilization of the event, whichever occurs first.~~

~~In case of lack of compliance or in case the patient is found not eligible, the patient discontinuation have to be discussed between Investigator and Sponsor.~~

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

~~If the patient needs to take one of the concomitant medications included in list of "Drugs with risk of Torsades de Pointes" (see Appendix C) the treatment with Givinostat is to be promptly discontinued and the patient must leave the study.~~

~~In case of multiple reasons (e.g. patient withdraws the consent for toxicity), "adverse events" should be indicated as the primary reason whenever applicable. All relevant information related to the reason for treatment discontinuation including contributory factors must be included on the 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. Should any drug related AE still be ongoing beyond the last scheduled visit, this must be followed at subsequent follow-up visits until recovery. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance every effort should 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 must be included on the CRF.~~

4.4.1 Investigational Medicinal Product (IMP)

Completed and updated data following described are reported in the Section 4 "Physical, chemical and pharmaceutical properties and formulation" of the current Investigator Brochure Dossier related to ITF2357.

Givinostat is a histone-deacetylases inhibitor.

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 Italfarmaco S.p.A. research code). Therefore, the dosages/concentrations of the study drug are expressed as Givinostat hydrochloride monohydrate.

The product will be supplied 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.

4.4.1.1 Dosage and administration

In *Part A* patients will 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, additionally DLs may be used to establish the MTD (for more details, see paragraph 4.1.1.3).

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

Dose adjustments are permitted for patients who do not tolerate the protocol-specified dosing schedule, in order to allow to these patients to continue the treatment with

Givinostat (see paragraph 4.3.3.1 and paragraph 4.3.3.2). 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 will self-administer daily Givinostat capsules at home as instructed by the Investigator (see paragraph 4.4.7.2 and paragraph 4.4.7.4), except for the first drug administration (i.e. Day 1 of the Cycle 1). Patients will not 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). Study drug will be 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 will 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 at 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 dosage (i.e. 50 mg b.i.d, or 100 mg b.i.d., or 150 mg/die), patients will self-administer daily Givinostat capsules at home at morning and at 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 can be dispensed to the patients is 100 mg b.i.d.. In all the possible dosage (i.e. 50 mg b.i.d., 75 mg b.i.d., 100 mg b.i.d.), patients will self-administer daily Givinostat capsules at home at morning and at 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 protocol-specified dosing schedule, in order to allow to these patients to continue the treatment with Givinostat. The guidelines described here above (i.e. see paragraph 4.3.3.2.1 and paragraph 4.3.3.2.2) 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 will be mandated for specific toxicities (see paragraph 4.3.3.2.1) and dose increases after an initial dose reduction will be allowed in the case of inadequate efficacy at the reduced dosage.
Each dose modification has to be recorded on the CRF.

~~4.4.1.2 Criteria for temporarily discontinuation~~
~~Study drug should be temporarily stopped in Cycles 2 and beyond of Part A of and in all Part B for any drug related grade 2 toxicity, despite adequate supportive care (where applicable).~~
~~In such cases, the following apply:~~

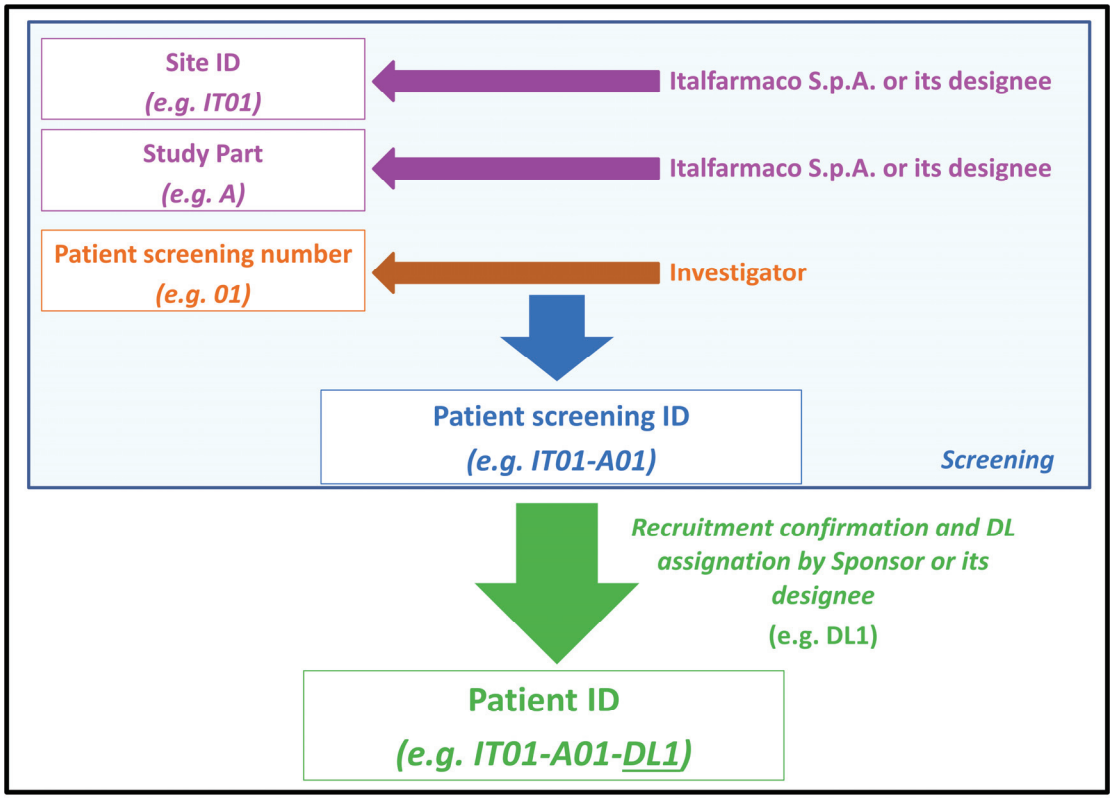
- ~~treatment with Givinostat must be promptly discontinued and the patient remains untreated until recovery of the observed toxicities to the level identified, as mandatory for treatment continuation;~~
- ~~in any event if recovery from previous toxicities takes 4 weeks or more, the experimental treatment shall not be restarted and the patient must discontinue the study.~~

~~Note that these temporary stopping rules will be applied only to drug-related AE's.~~
~~If vomiting occurs, no additional trial medication should be taken that day in an effort to replace the material that has been vomited.~~
~~If the patient inadvertently misses a drug dose, no additional trial medication should be taken that day or in the next days in the effort to replace the material that has been missed.~~

4.4.3 Patient numbering and screening

Each patient will be identified in the study by a patient code.
During the screening period (i.e. after the informed consent form signature and before the recruitment confirmation by the Italfarmaco S.p.A. or its designee), the patient code will be named patient screening ID and will be a combination of his/her site ID, study part ID and patient screening number.
Both the site ID and the study part ID (i.e. "A" or "B" for *Part A* or *Part B*, respectively) will be assigned by the Sponsor or its designee to the investigator site.
Upon signing the informed consent form, the patient screening number will be assigned by the Investigator. At each site, the first patient will be assigned patient number **"0**1**"**, and subsequent patients will be assigned consecutive numbers (e.g. the second patient will be assigned patient number **"0**2**"**, the third patient will be assigned patient number **"0**3**"**, etc**. etc.**).
When a study site has a patient ready to enrol, prior to dosing the site will compile a request for registration Form and send it to Italfarmaco S.p.A. or its designee in order to obtain the patient ID. The request for registration contains the site ID, the study part ID, the assigned patient screening number, a checklist related to the inclusion/exclusion criteria to verify the eligibility of the patient and collect some other information (e.g. date of birth, date of informed consent obtained). If the patient is eligible, Italfarmaco S.p.A. or its designee will confirm the enrolment of the patient assigning the related dose level and the patient ID (i.e. the patient code after the enrolment confirmation) which will be a combination of patient screening ID and dose level ID.
Once assigned, both the patient screening ID and the patient ID must not be reused for any other patient.

The following scheme will resume the patient identification process:



If the patient will fail to be enrolled for any reason, the reason will be entered in the study CRF within 2 days that the patient is not enrolled.
According to ICH-GCP guidelines, the Investigator will maintain a patient identification list, which ensures a distinctive identification of the patients by their name to screening numbers, date of birth, sex and date of inclusion.

4.4.6 Treatment compliance

The Investigator will record in the CRF the assigned dose of Givinostat and any dose reduction (if applicable) to allow the evaluation of compliance to treatment.
At each visit, patients will bring back to the study site all drug bottles previously received (**i.e.** used, partially used and unused) and receive a new supply. The number of residual capsules in the dispensed bottles will be counted by the Investigator and reported in the CRF.
Then the bottles used, partially used and unused will be collected and sent back to Italfarmaco S.p.A. **or their designee** periodically or at the end of the study.
Compliance with Givinostat treatment will be calculated by Italfarmaco S.p.A. or its designee based on the 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.

4.4.7 Drug supply

4.4.7.1 Packaging

The packaging will consist 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.

Depending on the need of supply of each Centre (e.g. number of treated patients) a variable number of bottles will be packed in a carton box for shipping.
At each visit, patients will receive a number of bottles sufficient to cover the period between two visits.

4.4.7.2 Labelling

The IMP will be appropriately labelled at Italfarmaco S.p.A. or their designee (e.g. external providers when requested by the local law, CMO).
Label of the bottles will comply with the legal requirements of each country and will be printed in the local language.
The labels will show all the information requested according to the Annex 13 to the Good Manufacturing Practice (published by the Commission in The rules governing medicinal products in the European Community, Volume 4) and the local drug law (if any) and the local regulatory requirements. Only the patient specific bottle will be labelled with a tear-off label.
The label of the medicinal product includes in the local language at least the following data:

- Sponsor's study code;
- EudraCT No.;
- Patient ID;
- Name, address and telephone number of the Sponsor or/and the CRO **or their delegates** (*if applicable*);
- Name of the Investigator;
- Name and strength of the medicinal product;
- Pharmaceutical dosage form;

- Route of administration;
- Quantity of dosage units;
- Visit in which the patient receive the study drug;
- Directions for use (reference may be made to a leaflet or other explanatory document intended for the trial patient or person administering the product);
- Batch number;
- Expiry date;
- Declaration of the intended purpose (e.g. for clinical trial use only);
- Storage conditions;
- The wording "Keep out of reach of children".

The patient ID and the visit in which the patient receive the study drug will be reported on every label by the Investigator.
The Investigator will also provide the patient with written instructions on the number of capsules to be taken at each administration (i.e. dosage schedule).

4.4.7.3 Storage

The IMP will be appropriately stored at Italfarmaco S.p.A. or **their** ~~its~~ designee (e.g. external providers when requested by the local law**, CMO**) until distribution to the investigational sites.
The investigational site will store the IMP under the same conditions, as specified in the label, ensuring that it is not accessible to unauthorized persons till its dispensing to patients.
Detailed instructions for the IMP storage and management will be provided in a separate and specific IMP handling instruction manual.

4.4.7.4 IMP dispensing

All IMP supplies are to be used only for this protocol and not for any other purpose.
Investigator will be responsible for the delivery of IMP to the patient according to the protocol **and to instruct the patient to take the IMP as per protocol**.
Patients will be administered the IMP on an outpatient basis.
At each visit, the Investigator will supply the patients with the appropriate number of bottles sufficient to cover the period between two visits.
The Investigator will also provide the patient with written instructions on the number of capsules to be taken at each administration.

4.4.7.5 IMP accountability

The Investigator will maintain accurate records of the disposition of all IMP received, distributed to patients (including date and time) and accidentally destroyed. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. At each visit, patients will bring back to the study site all drug bottles previously received (used, partially used and unused) and receive a new **IMP** supply.

At the study close-out, and, as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and the completed drug forms to Italfarmaco S.p.A., –Dipartimento di Tecnica Farmaceutica, Viale Fulvio Testi, 330, 20126 Milan (MI), Italy or its designee **(e.g. CMO)**.

Only in some particular cases, after the authorization of Italfarmaco S.p.A. (or after a signed agreement between the investigational site and Italfarmaco S.p.A.), these materials can be destroyed locally.

4.5.1 Laboratory evaluations and vital signs assessment

The laboratory examinations (haematology, blood chemistry and urinalysis) will be performed in the local laboratory of each site. In addition, the vital signs assessment, the ECG assessment/evaluation and the QTc determination (according with Bazett's correction formula, Appendix D) will be performed at each investigational site.

All these results will be transcribed into the CRF and the original signed and dated laboratory print-out/tracings, including the ECG and source document, will be monitored and stored at the study site. **Of note, if the first ECG evaluation demonstrates 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) must be performed. The averaged value of these three ECG evaluations has to be used for the evaluation of the QTc interval of the related visit. In the CRF all the performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*.**

The laboratory examinations, the vital signs assessment, the ECG evaluation including the QTc determination are listed below:

1) Haematology

   Red blood cells (RBC) count, haematocrit (HCT), haemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), white blood cells (WBC) count (full and differential), platelets (PLT) count.

2) Blood chemistry

   ALT/SGPT, AST/SGOT, alkaline phosphatase (ALP), total bilirubin, lactic dehydrogenase (LDH), creatinine, blood urea nitrogen (BUN) or Urea (see Appendix F to convert Urea to BUN), glucose, sodium (Na), potassium (K), calcium (Ca), chloride (Cl), magnesium (Mg), albumin**, eGFR determination (according with the Mayo Clinic Quadratic Equation)**.

3) Urinalysis

   pH, specific gravity, protein, glucose.

4) Vital signs

   Respiratory rate, pulse rate and sitting blood pressure will be measured after 5 minutes of rest.

5) ECG and QTc

   ECG assessment and evaluation, QTc determination (according with Bazett's correction formula, Appendix D). **Of note, if the first ECG evaluation demonstrates 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) must be performed. The averaged value of these three ECG evaluations has to be used for the evaluation of the QTc interval of the related visit. In the CRF all the performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*.**

4.5.3.1 Spleen evaluation

The spleen evaluation must be performed at the study centre according to the visit schedule outlined in the flow-chart (Appendix A).

The spleen evaluation will be performed during the study 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) should be used on a patient throughout the study, if possible.

If possible, the spleen dimension will be evaluated as longitudinal diameter (hereafter "A"), antero-posterior diameter (hereafter "B"), transversal diameter (hereafter "C") and Splenic Volumetric Index (hereafter "SVI"):

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

No spleen evaluation will be performed in splenectomised patients.

4.5.3.2 PK characterization

Approximately 5.0 mL of blood for pharmacokinetic assessment will be collected as following described:

1) Day 1 of Cycle 1 of *Parts A* and *B*: before the first Givinostat dose (pre-dose) and 2, 3 and 8 (before the second Givinostat dose) hours after the first drug administration (Appendix A).
   e.g.: the PK pre-dose evaluation will be performed at 7.45 a.m. of Day 1 (pre-dose) of Cycle 1 of *Parts A* and *B* and after that the patient will take the first drug administration (e.g. at 8.00 a.m.); then, the patient will perform the PK post-dose evaluations at 10.00 a.m. (hour 2), 11.00 a.m. (hour 3) and at 16.00 p.m. (hour 8).
2) Day 28 of the Cycle 1 of *Part A*: before the first daily Givinostat dose (pre-dose) and 1, 2, 4 and 8 (before the second Givinostat dose) after the first daily drug administration (Appendix A).
   e.g.: the PK pre-dose evaluation will be performed at 7.45 a.m. of Day 28 of Cycle 1 (pre-dose) of *Part A* and after that the patient will take the first daily drug administration (e.g. at 8.00 a.m.); then, the patient will perform the PK post-dose evaluations at 9.00 a.m. (hour 1), 10.00 a.m. (hour 2), 12.00 p.m. (hour 4) and at 16.00 p.m. (hour 8).
3) Day 28 of the Cycles 2, 3, 4, 5, and 6 of *Part A*: before the first daily Givinostat dose (pre-dose) (Appendix A).
   e.g.: the PK pre-dose evaluation will be performed at 7.45 a.m. of Day 28 of Cycle 2 and beyond Cycles (i.e. Cycles 3, 4, 5 and 6) of *Part A* (pre-dose) and after that the patient will take the first daily drug administration (e.g. at 8.00 a.m.).
4) Day 28 of Cycle 2 of *Part B*: before the first daily Givinostat dose (pre-dose) and 1, 2, 4 and 8 (before the second Givinostat dose) hours after the first daily drug administration (Appendix A).
   e.g.: the PK pre-dose evaluation will be performed at 7.45 a.m. of Day 28 of Cycle 2 (pre-dose) of *Part B* and after that the patient will take the first daily drug administration (e.g. at 8.00 a.m.); then, the patient will perform the PK post-dose evaluations at 9.00 a.m. (hour 1), 10.00 a.m. (hour 2), 12.00 a.m. (hour 4) and at 16.00 p.m. (hour 8).

The PK samples should be drawn as closely to the predefined time as possible.

The exact timing of PK sampling could be adjusted based on emerging clinical and preclinical data.

For all time points an additional PK blood sample will be collected as back-up sample.

This assessment is mandatory and will be performed by a central laboratory. The exact date and time of the PK blood draws will be recorded along with the date and time of the last dose of study drug preceding the blood draw. Additional information about the PK time points, instructions for sample preparation and shipment will be provided in the related study handling manual.

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.

4.5.3.3 PD characterization

Approximately 4.0 mL of blood for pharmacodynamic markers will be collected before the first Givinostat dose (pre-dose) and 12 hours after the first Givinostat dose (post-dose) at Day 1 of Cycle 1 both in *Part A* and in *Part B* for measurement of levels of molecular markers, to evaluate the pharmacodynamic effect of Givinostat and to identify markers predictive of clinical benefit of Givinostat (Appendix A). **In addition, pharmacodynamic evaluations will be performed also using an aliquot of the PK samples collected at time points described in the paragraph 4.5.3.2 [34].** 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 pharmacodynamic 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 will be collected as back-up sample.

This assessment is mandatory and will be performed by a central laboratory. The exact date and time of the PD blood draws will be recorded along with the date and time of the last dose of study drug preceding the blood draw. Instructions for sample preparation and shipment will be provided in a separate and specific laboratory manual.

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.

4.5.3.4 $JAK2^{V617F}$ characterization

$JAK2^{V617F}$ characterization (i.e. $JAK2^{V617F}$ allele burden evaluated by quantitative RT-PCR) will be performed in a central laboratory (Appendix E). Detailed instructions for sample preparation and shipment will be provided in a separate and specific laboratory manual.
For all time points a blood sample will be collected as back-up sample.

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.

4.5.4.1.1 Pre-treatment evaluations (up to 4 weeks: -28 to Day -1)

The following procedures will be performed at the pre-treatment visit of Cycle 1 of *Part A* as reported below:

- Informed consent signing;
- Demographic data (race, sex and date of birth);
- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (if applicable);
- Medical history;
- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), height, weight, body temperature and ECOG performance status;
- Pregnancy test (*if indicated*);
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN **or Urea** (**as per site-specific clinical practice;** see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin**, eGFR determination (according with the Mayo Clinic Quadratic Equation)**;
- ECG, QTc determination (according with Bazett's correction formula);
- Urinalysis: pH, specific gravity, protein, glucose;
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- Spleen evaluation by MRI or CT scan;
- Collection of a blood sample for the quantitative RT-PCR evaluation of JAK2V617F mutational status on peripheral blood (PB) granulocyte;
- Assessment of disease-related symptoms using the MPN-SAF QOL Questionnaire;
- Request of enrolment and receipt of patient ID.

Appendix A (in particular, paragraph 10.1.1.1) summarize timing information.

Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status [28] ≤ 1 within 7 days of initiating study drug.

The pregnancy test (if indicated) has to be 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 must be confirmed with a serum pregnancy test and the result recorded in the CRF.

~~Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status [28] ≤ 1 within 7 days of initiating study drug.~~

If the first ECG evaluation demonstrates 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) must be performed. The averaged value of these three ECG

evaluations has to be used for the evaluation of the QTc interval requested by the exclusion criterion n. 3. In the CRF all the performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*.

Patients with splenomegaly will perform the spleen evaluation as per site-specific clinical practice. Therefore, patients with splenomegaly before the treatment start will be followed according to institutional guidelines (i.e. MRI or CT scan). The same imaging technique and the same instrument should be used on a patient throughout the study, *if possible*. **No spleen evaluation will be performed in splenectomised patients.**

Pre-treatment evaluations will be performed at one or more clinic visit to determine eligibility for the study. Pre-treatment evaluations must be performed up to 4 weeks before the treatment start within ± 7 days.

If all eligibility criteria are met at the pre-treatment visit, the treatment with Givinostat can start.

After the check that all eligibility criteria are met by the patient and in any case before the treatment start, all patients with an uncontrolled HCT (i.e. HCT ≥ 45%) have to perform at least one phlebotomy to normalize (if possible) the HCT value (i.e. HCT <45%).

In case of patients phlebotomy-dependent, all efforts have to be afforded by Investigators to record all phlebotomies witch recruited patients experienced at least 6 months before the treatment start.

4.5.4.1.2 Cycle 1

Appendix A (in particular, paragraph 10.1.1.1) summarize timing information.

Patients can take drug at home, except for the first drug administration.

If the first ECG evaluation demonstrates 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) must be performed. The averaged value of these three ECG evaluations has to be used for the evaluation of the QTc interval. In the CRF all the performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*.

Day 1

The following procedures must be performed exactly at Day 1 of Cycle 1 of ***Part A*** as reported below:

1) Pre-dose evaluations:

   The following procedures will be performed before the first Givinostat dose as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
- Physical examination, weight, body temperature and ECOG performance status;
- Vital signs (blood pressure, pulse rate, respiratory rate);
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN **or Urea** (**as per site-specific clinical practice;** see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin**, eGFR determination (according with the Mayo Clinic Quadratic Equation)**;
- ECG, QTc determination (according with Bazett's correction formula);
- PD sample collection;
- PK sample collection **and preparation, in order to allow to perform both the PK and PD evaluations starting from the same sample [34]**.

2) Post-dose evaluations:

The following procedures will be performed after the first Givinostat dose as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
- Vital signs (blood pressure, pulse rate, respiratory rate) *4 hours after the first Givinostat dose*;
- ECG, QTc determination (according with Bazett's correction formula) *3 hours after the first Givinostat dose*;
- PD sample collection *12 hours after the first Givinostat dose*;
- PK sample collection (2, 3 and 8 hours post-dose) **and preparation, in order to allow to perform both the PK and PD evaluations starting from the same sample [34]**;
- First Givinostat dose and accountability.

Day 2

The following procedures will be performed exactly at Day 2 of Cycle 1 of ***Part A*** as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status;
- ECG, QTc determination (according with Bazett's correction formula);
- **Used/unused/partially used Givinostat supply return,** Givinostat administration and **Givinostat** accountability.

Days 3 and 4

The following procedures will be performed exactly at Days 3 and 4 of Cycle 1 of *Part A* as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
- **Used/unused/partially used Givinostat supply return,** Givinostat administration and **Givinostat** accountability.

Days 8, 15 and 22

The following procedures will be performed at Days 8, 15 and 22 of Cycle 1 of *Part A* (within ± 3 days) as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status;
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN **or Urea (as per site-specific clinical practice;** see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin**, eGFR determination (according with the Mayo Clinic Quadratic Equation)**;

- ECG, QTc determination (according with Bazett's correction formula);
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- **Used/unused/partially used Givinostat supply return,** Givinostat administration and **Givinostat** accountability.

Day 10

The following procedures will be performed at Day 10 of Cycle 1 of *Part A* (within ± 3 days) as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
- **Used/unused/partially used Givinostat supply return,** Givinostat administration and **Givinostat** accountability.

Days 28

The following procedures will be performed at Day 28 of Cycle 1 of *Part A* (within ± 3 days) as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status;
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN **or Urea (as per site-specific clinical practice;** see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin**, eGFR determination (according with the Mayo Clinic Quadratic Equation)**;
- ECG, QTc determination (according with Bazett's correction formula);
- Urinalysis: pH, specific gravity, protein, glucose;
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;

- PK sample collection (pre-dose and 1, 2, 4 and 8 hours post-dose) **and preparation, in order to allow to perform both the PK and PD evaluations starting from the same sample [34]**;
- **Used/unused/partially used Givinostat supply return,** Givinostat administration and **Givinostat** accountability.

End of Study

In case of the patient drops-out of the study, the following procedures will be performed 7 days after last drug intake (within ± 3 days) as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status;
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN **or Urea (as per site-specific clinical practice;** see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin**, eGFR determination (according with the Mayo Clinic Quadratic Equation)**;
- ECG, QTc determination (according with Bazett's correction formula);
- Urinalysis: pH, specific gravity, protein, glucose;
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- Spleen evaluation by MRI or CT scan;
- Therapeutic response evaluation according to the clinico-haematological ELN response criteria [21] (see paragraph 4.6.1);
- Assessment of disease-related symptoms using the MPN-SAF QOL Questionnaire;
- Used/unused/partially used Givinostat supply return and **Givinostat** accountability.

As reported also in the paragraph 4.3.3, if the patient discontinues for any reason (including discontinuation for pregnancy), with drug related adverse event ongoing at study end, he/she must be followed until resolution or stabilization of the event or until it is reasonable to consider the event not drug related any more or until the start of a new treatment, whichever occurs first.

If the patient needs to take one of the concomitant medications included in list of "Drugs with risk of Torsades de Pointes" (see Appendix C) the treatment with Givinostat is to be promptly discontinued and the patient must leave the study.
In case of multiple reasons (e.g. patient withdraws the consent for toxicity), "adverse events" should be indicated as the primary reason whenever applicable. All relevant information related to the reason for treatment discontinuation including contributory factors must be included on the 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. Should any drug-related AE still be ongoing beyond the last scheduled visit, this must be followed at subsequent follow-up visits until recovery. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance every effort should 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 must be included on the CRF.

At study close-out, and as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and the completed drug forms to Italfarmaco S.p.A., –Dipartimento di Tecnica Farmaceutica, Viale Fulvio Testi, 330, 20126 Milan **(MI)**, Italy, or **their** designee.

Only in some particular cases, after the authorization of Italfarmaco S.p.A. (or after a signed agreement between the investigational site and Italfarmaco S.p.A.), these materials can be destroyed locally.

4.5.4.1.3 Cycles 2, 3, 4, 5 and 6

Appendix A (in particular, paragraph 10.1.1.2) summarize timing information.

Patients with splenomegaly will perform the spleen evaluation as per site-specific clinical practice. Therefore, patients with splenomegaly before the treatment start will be followed according to institutional guidelines (i.e. MRI or CT scan). The same imaging technique and the same instrument should be used on a patient throughout the study, if possible. **No spleen evaluation will be performed in splenectomised patients. The spleen evaluation must be performed at the study centre according to the visit schedule outlined in the flow-chart (Appendix A).**

If the first ECG evaluation demonstrates 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) must be performed. The averaged value of these three ECG evaluations has to be used for the evaluation of the QTc interval. In the CRF all the

performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*.

Day 1

The following procedures will be performed at Day 1 of Cycles 2, 3, 4, 5 and 6 of *Part A* (within ± 3 days) as reported below:

- First Givinostat dose of the related cycle and accountability.

Day 28 of Cycles 2, 4 and 5

The following procedures will be performed at Day 28 of Cycles 2, 4 and 5 of *Part A* (within ± 3 days) as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status;
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN **or Urea** (**as per site-specific clinical practice;** see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin**, eGFR determination (according with the Mayo Clinic Quadratic Equation)**;
- ECG, QTc determination (according with Bazett's correction formula);
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- PK sample collection (pre-dose) **and preparation, in order to allow to perform both the PK and PD evaluations starting from the same sample [34]**;
- **Used/unused/partially used Givinostat supply return,** Givinostat administration and **Givinostat** accountability.

Day 28 of Cycles 3 and 6

The following procedures will be performed at Day 28 of Cycles 3 and 6 of *Part A* (within ± 3 days) as reported below:

- Adverse event recording;
- Concomitant medications (drugs);

- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status;
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN **or Urea** (**as per site-specific clinical practice;** see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin**, eGFR determination (according with the Mayo Clinic Quadratic Equation)**;
- ECG, QTc determination (according with Bazett's correction formula);
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- PK sample collection (pre-dose) **and preparation, in order to allow to perform both the PK and PD evaluations starting from the same sample [34]**;
- Spleen evaluation by MRI or CT scan;
- Therapeutic response evaluation according to the clinico-haematological ELN response criteria [21] (see paragraph 4.6.1);
- Collection of a blood sample for the quantitative RT-PCR evaluation of $JAK2^{V617F}$ mutational status on peripheral blood (PB) granulocyte;
- Assessment of disease-related symptoms using the MPN-SAF QOL Questionnaire;
- **Givinostat administration (only for *cycle 3*);**
- **Used/unused/partially used Givinostat supply return**~~Givinostat administration~~ and **Givinostat** accountability.

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 [21] (see paragraph 4.6.1);.

End of Study

The following procedures will be performed at the end of study visit (in case of completed study) or 7 days after last drug intake (in case of the patient drops-out of the study) (within ± 3 days) as reported below:

- Adverse event recording;
- Concomitant medications (drugs);

- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status;
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN **or Urea** (**as per site-specific clinical practice;** see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin**, eGFR determination (according with the Mayo Clinic Quadratic Equation)**;
- ECG, QTc determination (according with Bazett's correction formula);
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- Spleen evaluation by MRI or CT scan;
- Therapeutic response evaluation according to the clinico-haematological ELN response criteria [21] (see paragraph 4.6.1);
- Collection of a blood sample for the quantitative RT-PCR evaluation of $JAK2^{V617F}$ mutational status on peripheral blood (PB) granulocyte;
- Assessment of disease-related symptoms using the MPN-SAF QOL Questionnaire;
- Used/unused/partially used Givinostat supply return and accountability.

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 the Cycle 6 Day 28 visit can be counted for the End of Study visit.

In addition, in case the patient completes the study (i.e. performs all the evaluations requested to be done at the Day 28 of Cycle 6) and she/he is eligible to continue the study drug treatment in the long-term study (i.e. Study DSC/11/2357/44), the evaluation performed at the Cycle 6 Day 28 visit of this study can be also counted for the pre-treatment evaluations of the Study DSC/11/2357/44, provided that no difference in the evaluation is present between the two studies (e.g. haematological and biochemical evaluations). No additional Givinostat study (i.e. Study DSC/12/2357/45)-specific assumption has to be done at the completion of the Day 28 of Cycle 6. Indeed, in case the patient completes the study (i.e. performs all the evaluations requested to be done at the Day 28 of Cycle 6 of this study), she/he is eligible to continue the study drug treatment in the long-term study (i.e. Study DSC/11/2357/44) and she/he receive the written authorization of the treatment from the Sponsor of their designee (i.e. a patient's confirmation form that includes the patient ID to use into the Study DSC/11/2357/44), the patient will continue the study drug treatment into the Study DSC/11/2357/44, receiving the study (i.e. Study DSC/11/2357/44)-specific drug to be taken.

As reported also in the paragraph 4.3.3, if the patient discontinues for any reason (including discontinuation for pregnancy), with drug related adverse event ongoing at study end, he/she must be followed until resolution or stabilization of the event or until it is reasonable to consider the event not drug related any more or until the start of a new treatment, whichever occurs first.
If the patient needs to take one of the concomitant medications included in list of "Drugs with risk of Torsades de Pointes" (see Appendix C) the treatment with Givinostat is to be promptly discontinued and the patient must leave the study.
In case of multiple reasons (e.g. patient withdraws the consent for toxicity), "adverse events" should be indicated as the primary reason whenever applicable. All relevant information related to the reason for treatment discontinuation including contributory factors must be included on the 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. Should any drug-related AE still be ongoing beyond the last scheduled visit, this must be followed at subsequent follow-up visits until recovery. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance every effort should 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 must be included on the CRF.

At study close-out, and as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and the completed drug forms to Italfarmaco S.p.A.**,** Dipartimento di Tecnica Farmaceutica, Viale Fulvio Testi, 330, 20126 Milan **(MI)**, Italy, or **their**~~its~~ designee.

Only in some particular cases, after the authorization of Italfarmaco S.p.A. (or after a signed agreement between the investigational site and Italfarmaco S.p.A.), these materials can be destroyed locally.

4.5.4.2 *Part B*

Appendix A (in particular, paragraph 10.1.2) summarize timing information.

Patients should be told to arrive after an overnight fast of at least 8 hours at all study visits that request a blood test. However, the study visits should still be conducted even if the patient does not adhere to fasting requirements and this will not be considered a protocol violation. In these cases, this information (i.e. not fasting condition) has to be noted by the Investigator in the medical chart and reported in CRF, in order to avoid any misunderstanding of the collected data (e.g. glucose value is influenced by fasting/ not fasting conditions).

If the first ECG evaluation demonstrates 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) must be performed. The averaged value of these three ECG evaluations has to be used for the evaluation of the QTc interval. In the CRF all the performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*.

The spleen evaluation ~~Patients with splenomegaly~~ will **be** perform**ed during the study according to institutional guidelines and** ~~the spleen evaluation as per~~ **site-specific clinical practice (i.e. MRI or CT scan)**. ~~Therefore, patients with splenomegaly before the treatment start will be followed according to institutional guidelines (i.e. MRI or CT scan).~~ The same imaging technique and the same instrument should be used on a patient throughout the study, *if possible*. **No spleen evaluation will be performed in splenectomised patients.**

Patients can take drug at home, except for the first drug administration.

4.5.4.2.1 Pre-treatment evaluations (up to 4 weeks: -28 to Day -1)

The following procedures will be performed at the pre-treatment visit of *Part B* as reported below:

- Informed consent signing;
- Demographic data (race, sex and date of birth);
- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
- Medical history;
- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), height, weight, body temperature and ECOG performance status;
- Pregnancy test (*if indicated*);
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN **or Urea** (**as per site-specific clinical practice;** see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin**, eGFR determination (according with the Mayo Clinic Quadratic Equation)**;
- ECG, QTc determination (according with Bazett's correction formula);
- Urinalysis: pH, specific gravity, protein, glucose;

- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- Spleen evaluation by MRI or CT scan;
- Collection of a blood sample for the quantitative RT-PCR evaluation of $JAK2^{V617F}$ mutational status on peripheral blood (PB) granulocyte;
- Assessment of disease-related symptoms using the MPN-SAF QOL Questionnaire [24, 32];
- Bone marrow histological evaluation, in patients who have consented to this optional exploratory research, who haven't this assessment in the month before the 1 month before the study start (i.e the signature of the Informed Consent Form, and that have not any medical contraindication to bone marrow sampling as judged by the Investigator);
- Request of enrolment and receipt of patient ID.

Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status [28] ≤ 2 within 7 days of initiating study drug.

The pregnancy test (*if indicated*) has to be 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 must be confirmed with a serum pregnancy test and the result recorded in the CRF.

~~Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status [28] ≤ 2 within 7 days of initiating study drug.~~

~~Patients with splenomegaly will perform the spleen evaluation as per site-specific clinical practice. Therefore, patients with splenomegaly before the treatment start will be followed according to institutional guidelines (i.e. MRI or CT scan). The same imaging technique and the same instrument should be used on a patient throughout the study, *if possible*.~~

Pre-treatment evaluations will be performed at one or more clinic visit to determine eligibility for the study. Pre-treatment evaluations must be performed up to 4 weeks before the treatment start within ± 7 days.

Please note that, in case the patient performs the bone marrow histological evaluation as requested by the "new" ELN criteria (i.e. the revised ELN response criteria) [33] (see paragraph 4.8.7) – 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 Informed Consent Form), 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 will

be transcribed into the 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, will be monitored and stored at the study site.

In case the patient refuses to provide this written consent to perform the bone marrow evaluation, this patient can be anyway 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 [33], and the evaluation of the effect of Givinostat on each single response parameter according to the revised ELN response criteria [33]).

If all eligibility criteria are met at the pre-treatment visit, the treatment with Givinostat can start.

After the check that all eligibility criteria are met by the patient and in any case before the treatment start, all patients with an uncontrolled HCT (i.e. HCT ≥ 45%) have to perform phlebotomy(ies) to normalize the HCT value (i.e. HCT <45%).

In case of patients **who are** phlebotomy-dependent, all efforts have to be made by Investigators to record all phlebotomies witch recruited patients experienced at least 6 months before the treatment start.

4.5.4.2.2 Day 1 of Cycle 1

The following procedures must be performed exactly at Day 1 of Cycle 1 of ***Part B*** as reported below:

1) Pre-dose evaluations:

   The following procedures will be performed before the first Givinostat dose as reported below:

   - Adverse event recording;
   - Concomitant medications (drugs);
   - Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
   - PD sample collection;
   - PK sample collection **and preparation, in order to allow to perform both the PK and PD evaluations starting from the same sample [34] (*if requested*)**.

2) Post-dose evaluations:

The following procedures will be performed after the first Givinostat dose as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
- PD sample collection *12 hours after the first Givinostat dose*;
- PK sample collection (2, 3 and 8 hours post-dose) **and preparation, in order to allow to perform both the PK and PD evaluations starting from the same sample [34] (*if requested*)**;
- First Givinostat dose and accountability.

4.5.4.2.3 Day 28 of Cycles 1, 2, 4 and 5

The following procedures will be performed at Day 28 of Cycles 1, 2, 4 and 5 of *Part B* (within ± 3 days) as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status;
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN **or Urea** (**as per site-specific clinical practice;** see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin, eGFR determination (according with the Mayo Clinic Quadratic Equation);
- ECG, QTc determination (according with Bazett's correction formula);
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- **Collection of a blood sample for the quantitative RT-PCR evaluation of JAK2^{V617F} mutational status on peripheral blood (PB) granulocyte;**
- **Used/unused/partially used Givinostat supply return, Givinostat administration and Givinostat accountability;**

- ***Only at Cycle 2:*** PK sample collection (pre-dose and 1, 2, 4 and 8 hours post-dose) **and preparation, in order to allow to perform both the PK and PD evaluations starting from the same sample [34] (*if requested*)**~~at Cycle 2 only;~~**.**
- ~~Givinostat administration and accountability.~~

4.5.4.2.4 Day 28 of Cycles 3 and 6

The following procedures will be performed at Day 28 of Cycles 3 and 6 of *Part B* (within ± 3 days) as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status;
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN **or Urea** (**as per site-specific clinical practice;** see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin**, eGFR determination (according with the Mayo Clinic Quadratic Equation)**;
- ECG, QTc determination (according with Bazett's correction formula);
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- Spleen evaluation by MRI or CT scan;
- Collection of a blood sample for the quantitative RT-PCR evaluation of $JAK2^{V617F}$ mutational status on peripheral blood (PB) granulocyte;
- Assessment of disease-related symptoms using the MPN-SAF QOL Questionnaire [24, 32];
- Bone marrow histological evaluation (only for *cycle 6*) in patients who have consented to this optional exploratory research and that have not any medical contraindication to bone marrow sampling as judged by the Investigator;
- Therapeutic response evaluation according to the clinico-haematological ELN response criteria [21] (see paragraph 4.6.1);

- Therapeutic response evaluation according to the "new" ELN criteria (i.e. revised ELN response criteria) [33] (see paragraph 4.8.7) (only for *cycle 6*);
- ***Only for Cycle 3:*** Givinostat administration;
- **Used/unused/partially used Givinostat supply return, and** Givinostat ~~a~~**dministration****countability** ~~and accountability (only for cycle 3)~~.

All phlebotomies performed in the first 3 weeks of treatment will be not counted to assess the therapeutic response.

4.5.4.2.5 End of study

The following procedures will be performed at the end of study visit (in case of completed study) or 7 days after last drug intake (in case of the patient drops-out of the study) (within ± 3 days) as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (*if applicable*);
- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status;
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN **or Urea** (**as per site-specific clinical practice;** see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin**, eGFR determination (according with the Mayo Clinic Quadratic Equation)**;
- ECG, QTc determination (according with Bazett's correction formula);
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- Spleen evaluation by MRI or CT scan;
- Collection of a blood sample for the quantitative RT-PCR evaluation of $JAK2^{V617F}$ mutational status on peripheral blood (PB) granulocyte;

- Assessment of disease-related symptoms using the MPN-SAF QOL Questionnaire [24, 32];
- Bone marrow histological evaluation, in patients who have consented to this optional exploratory research, and that have not any medical contraindication to bone marrow sampling as judged by the Investigator;
- Therapeutic response evaluation according to the clinico-haematological ELN response criteria [21] (see paragraph 4.6.1);
- Therapeutic response evaluation according to the "new" ELN criteria (i.e. revised ELN response criteria) [33] (see paragraph 4.8.7);
- Used/unused/partially used Givinostat supply return and **Givinostat** accountability.

In case the patient drops-out the study during the first 3 Cycles (i.e. before the Day 28 of Cycle 3), the **bone marrow histological evaluation** ~~is~~ has not to be performed at End of Study visit.

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 the Cycle 6 Day 28 visit can be counted for the End of Study visit.

In addition, in case the patient completes the study (i.e. performs all the evaluations requested to be done at the Day 28 of Cycle 6) and she/he is eligible to continue the study drug treatment in the long-term study (i.e. Study DSC/11/2357/44), the evaluation performed at the Cycle 6 Day 28 visit of this study can be also counted for the pre-treatment evaluations of the Study DSC/11/2357/44, provided that no difference in the evaluation is present between the two studies (e.g. haematological and biochemical evaluations). No additional Givinostat study (i.e. Study DSC/12/2357/45)-specific assumption has to be done at the completion of the Day 28 of Cycle 6. Indeed, in case the patient completes the study (i.e. performs all the evaluations requested to be done at the Day 28 of Cycle 6 of this study), she/he is eligible to continue the study drug treatment in the long-term study (i.e. Study DSC/11/2357/44) and she/he receive the written authorization of the treatment from the Sponsor of their designee (i.e. a patient's confirmation form that includes the patient ID to use into the Study DSC/11/2357/44), the patient will continue the study drug treatment into the Study DSC/11/2357/44, receiving the study (i.e. Study DSC/11/2357/44)-specific drug to be taken.

As reported also in the paragraph 4.3.3, if the patient discontinues for any reason (including discontinuation for pregnancy), with drug related adverse event ongoing at study end, he/she must be followed until resolution or stabilization of the event or until it is reasonable to consider the event not drug related any more or until the start of a new treatment, whichever occurs first.

If the patient needs to take one of the concomitant medications included in list of "Drugs with risk of Torsades de Pointes" (see Appendix C) the treatment with Givinostat is to be promptly discontinued and the patient must leave the study.

In case of multiple reasons (e.g. patient withdraws the consent for toxicity), "adverse events" should be indicated as the primary reason whenever applicable. All relevant information related to the reason for treatment discontinuation including contributory factors must be included on the 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. Should any drug-related AE still be ongoing beyond the last scheduled visit, this must be followed at subsequent follow-up visits until recovery. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance every effort should 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 must be included on the CRF.

At study close-out, and as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and the completed drug forms to Italfarmaco S.p.A., —Dipartimento di Tecnica Farmaceutica, Viale Fulvio Testi, 330, 20126 Milan **(MI)**, Italy **or their designee**.

Only in some particular cases, after the authorization of Italfarmaco S.p.A. (or after a signed agreement between the investigational site and Italfarmaco S.p.A.), these materials can be destroyed locally.

4.6.1 Criteria for assessing clinico-haematological improvement

Disease response will be evaluated according to the following clinico-haematological ELN criteria [21] (see paragraph 4.6.1) 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. **P~~p~~**latelets ≤ 400 x10^9/L, and
  3. WBC ≤10 x10^9/L, and
  4. Normal spleen size, and
  5. **N~~n~~o** 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. **R~~r~~**esponse 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 will be evaluated according to the clinico-haematological ELN and EUMNET criteria [29] after 3 and 6 cycles of treatment with Givinostat, in ET and MF patients, respectively.

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

- *Complete response:*
  1. **P~~p~~**latelets ≤ 400 x10^9/L, and
  2. **N~~n~~**o disease related systemic symptoms (i.e. pruritus, headache, microvascular disturbances), and
  3. **N~~n~~**ormal 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 will not be 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 x10^9/L or platelet count increase by ≥ 50% x 10^9/L if baseline < 100 x10^9/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 hemoglobin 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 will be evaluated directly by patients according to MPN-SAF QOL questionnaire [24, 32].
In all cases, the response status of the patient may be reviewed by a panel of independent Investigators, *if necessary*.

4.6.3 Criteria for characterization of PK

Plasma concentrations from *Parts A* and *B* will be evaluated by dose and time point for all patients and time points with at least **one** ~~1~~ PK assessment.

4.6.4 The Efficacy Population

The analysis sets are defined in the paragraph 6.2.1.

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 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 ~~if necessary~~ by a panel of independent investigators***, if necessary***.

4.7.1 Laboratory evaluations

The following laboratory examinations (haematology, blood chemistry and urinalysis) will be 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;** see Appendix F to convert Urea to BUN) , glucose, Na, K, Ca, Cl, Mg, albumin**, eGFR determination (according with the Mayo Clinic Quadratic Equation)**;
- Urinalysis: pH, specific gravity, protein, glucose.

The required amount of blood and urine will be collected at each visit as scheduled above. Appendix A and paragraph 4.5.4 summarize timing information.

All results of laboratory examinations will be entered into the appropriate CRF sections. The original laboratory print-outs will be filed in the patient file at the study site.

Of note, if the ECG evaluation demonstrates 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) must be performed. The averaged value of these three ECG evaluations has to be used for the evaluation of the QTc interval of the related visit. In the CRF all the performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*.

4.7.2 Clinical safety assessments

Clinical safety assessments will include a thorough physical examination, vital signs assessment (respiratory rate, pulse rate and sitting blood pressure will be measured after 5 minutes of rest),

weight, body temperature, ECOG performance status, ECG assessment and evaluation, QTc determination (according with Bazett's correction formula, Appendix D).

Appendix A and paragraph 4.5.4 summarize timing information.

All results of the above mentioned clinical safety assessments will be entered into the appropriate CRF sections. The original print-outs related to these evaluations, including the ECG and QTc recording, will be filed in the patient file at the study site.

Of note, if the ECG evaluation demonstrates 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) must be performed. The averaged value of these three ECG evaluations has to be used for the evaluation of the QTc interval of the related visit. In the CRF all the performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*.

4.7.3 Adverse events

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

~~For AEs definitions, coding and reporting procedures see paragraph 5.~~

As reported also in the paragraph 4.3.3, if the patient discontinues for any reason (including discontinuation for pregnancy), with drug related adverse event ongoing at study end, he/she must be followed until resolution or stabilization of the event or until it is 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 events" should be indicated as the primary reason whenever applicable. All relevant information related to the reason for treatment discontinuation including contributory factors must be included on the 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. Should any drug-related AE still be ongoing beyond the last scheduled visit, this must be followed at subsequent follow-up visits until recovery. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance every effort should 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 must be included on the CRF.

For AEs definitions, coding and reporting procedures see paragraph 5.

4.8.3 Spleen size assessment

The spleen evaluation must be performed at the study centre according to the visit schedule outlined in the flow-chart (Appendix A).

To evaluate the effects of Givinostat on spleen size ~~(by MRI or CT scan) in patients with confirmed splenomegaly before the treatment start~~ will be used MRI or CT scan.

The spleen evaluation ~~Patients with splenomegaly~~ will **be performed** ~~followed~~ 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 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) should be used on a patient throughout the study, *if possible*.

If possible, the spleen dimension will be evaluated as longitudinal diameter (hereafter "A"), antero-posterior diameter (hereafter "B"), transversal diameter (hereafter "C") and Splenic Volumetric Index (hereafter "SVI"):

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

4.8.4 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) will be used in ***Parts A*** **and** ***B***, in order to assess the most important clinical symptoms among patients with MPNs [24].

In addition, starting from MPN-SAF questionnaire, **in** ***Part B*** also the MPN-SAF Total Symptom Score [32] will be assessed as requested by the "new" ELN criteria (i.e. revised ELN response criteria) [32].

4.8.8 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) [33] (see paragraph 4.8.7) will be used to evaluate the effect of Givinostat in PV patients **in** ***Part B***.

5. ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of AEs as defined in this protocol. AE data will be obtained at all study visits, based on information spontaneously provided by the patient and/or through questioning. Additionally, patients will be advised that they can contact the Investigator at any time to report or discuss AEs.

As reported also in the paragraph 4.3.3, if the patient discontinues for any reason (including discontinuation for pregnancy), with drug related adverse event ongoing at study end, he/she must be followed until resolution or stabilization of the event or until it is 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 events" should be indicated as the primary reason whenever applicable. All relevant information related to the reason for treatment discontinuation including contributory factors must be included on the 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. Should any drug-related AE still be ongoing beyond the last scheduled visit, this must be followed at subsequent follow-up visits until recovery. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance every effort should 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 must be included on the CRF.

5.1.1 Adverse Event (AE)

An Adverse Event is "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment" (ICH E2A).

AEs include:

- Onset of any clinical sign or symptom**;**
- Worsening (change in nature, severity or frequency) of conditions present at the start of the trial**;**
- Patient deterioration due to the primary illness**;**
- Intercurrent illnesses**;**
- Drug interactions**;**

- Events related or possibly related to concomitant medications**;**
- Abnormal laboratory values, as well as significant shifts from baseline within the range of normal, which the investigator considers to be clinically significant.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

5.1.2 Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product **or its new usages, particularly as the therapeutic dose(s) may not be established**: "all noxious and unintended responses to a medicinal product related to any dose should be considered Adverse Drug Reaction".
The phrase "responses to a medicinal products" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.
Regarding marketed medicinal products, a well-accepted definition of an adverse drug reaction in the post-marketing setting is found in WHO Technical Report 498 [1972] and reads as follows: "a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function."
The old term "side effect" has been used in various ways in the past, usually to describe negative (unfavourable) effects, but also positive (favourable) effects. It is recommended that this term no longer be used and particularly should not be regarded as synonymous with adverse event or adverse reaction.

5.1.3 Unexpected Adverse Drug Reaction
An Unexpected Adverse Drug Reaction is "a~~A~~n Adverse Drug Reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational medicinal product or summary of product characteristics, SPC, for marketed products)".
All adverse events judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

5.1.4 Serious Adverse Event (SAE)

A Serious Adverse Event (experience) or reaction is **"**any untoward medical occurrence that at any dose:

- **results** is fatal (results in the outcome death);
- is life-threatening*;
- required in-patient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is medically significant or requires intervention to prevent one or other of the outcomes listed above;
- consists in the transmission of an infective agent through the IMP."

**The term life-threatening refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event which hypothetically may cause death if it is more severe.*

Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/ reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.
The pre-planned hospitalization or adverse reaction expected as part of the trial treatment (e.g. standard expected side effect of chemotherapy) should not considered as SAE.
A Suspected Unexpected Serious Adverse Reaction (SUSAR) is referred to an adverse drug reaction which comply with both the definitions of "serious" and "unexpected".

5.2 AE Reporting

The Investigators or their designees are requested to collect and asses any spontaneous AE reported by the patient and to question the patient about AEs and undercurrent illnesses at each visit during the treatment period and **any** follow-up **visit performed to monitor any drug-related AE that is still ongoing beyond the last scheduled visit until recovery**. The questioning of patients regarding AEs is generalized such as "*How have you been feeling since your last visit?*" Any AE occurring after a patient has signed the Informed Consent form and up to the follow-up study visit, whether volunteered by the patient, discovered during general

questioning by the Investigators or detected through physical examination, laboratory test or other means, will be recorded on the specific section of the CRF. Each AE will be described by:

- *the seriousness;*
- *the duration (start and end dates);*
- *the severity;*
- *the relationship with the IMP;*
- *the action taken.*

The severity of AE should be assessed and graded according to the most recently published NCI Common Terminology Criteria for AE (CTCAE v. 4.03, 14th June 2010).

The relationship with the IMP should be assessed as:

- *related to IMP;*
- *not related to IMP;*
- *unknown.*

The assessment of the relationship of an adverse event with the administration of IMP is a clinical decision based on all available information at the time of the completion of the CRF.

An assessment of **"***Not related***"** would include the existence of a clear alternative explanation, or non-plausibility.

An assessment of **"***Related***"** indicates that there is a reasonable suspicion that the adverse event is associated with the use of the IMP.

An assessment "*Unknown*" indicates there is not a reasonable suspicion that the adverse event is associated with the use of the IMP and at the same time there is not the existence of a clear alternative explanation or non-plausibility. In this case, Investigator has to collect all possible information in order to assess the relationship with the IMP, particularly in case of Serious Adverse Events.

Factors to be considered in assessing the relationship of the adverse event to study drug include:

- *The temporal sequence from IMP administration;*
- *The recovery on discontinuation and recurrence on reintroduction;*
- *The concomitant diseases;*
- *The evolution of the treated disease;*
- *The concomitant medication;*
- *The pharmacology and pharmacokinetics of the IMP;*
- *The presence of an alternative explanation.*

5.2.1 Abnormal laboratory findings and other objective measurements

Abnormal laboratory findings and other objective measurements should not be routinely captured and reported as AEs as they will be collected and analysed separately in the CRF. However, abnormal laboratory findings and other objective measurements that meet the criteria for an SAE, result in discontinuation of the IMP or require medical intervention, or are judged by the Investigator to be clinically significant changes from baselines values should be captured and reported on the AE pages of the CRF.

As reported also in the paragraph 4.3.3, if the patient discontinues for any reason (including discontinuation for pregnancy), with drug related adverse event ongoing at study end, he/she must be followed until resolution or stabilization of the event or until it is 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 events" should be indicated as the primary reason whenever applicable. All relevant information related to the reason for treatment discontinuation including contributory factors must be included on the 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. Should any drug-related AE still be ongoing beyond the last scheduled visit, this must be followed at subsequent follow-up visits until recovery. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance every effort should 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 must be included on the CRF.

When reporting an abnormal laboratory finding on the AE pages of the CRF, a clinical diagnosis should be recorded in addition to the abnormal value itself, if this is available (for example "anaemia" in addition to "haemoglobin = 10.5 g/dl").

5.3 SAE Reporting

Any SAE, including death from any cause that occurs after a patient has signed the Informed Consent and up to **any** ~~the~~ follow-up **visit performed to monitor any drug-related AE that is still ongoing beyond the last scheduled visit until recovery** (regardless of relationship to study drug) must be reported by the Investigators to Italfarmaco S.p.A. within 24 hours of learning of its occurrence.

Related SAEs MUST be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed. **Anyway, no active subject monitoring by the Investigators is required.**

The Investigators are required to complete the SAE ~~f~~**F**orm**, according with the procedures described in the study manual and within 24 hours of learning of its occurrence** ~~provided by Italfarmaco S.p.A.~~. Sufficient details must be provided to allow for a complete medical assessment of the AE and independent determination of possible causality. The Investigators are obliged to pursue and provide additional information as requested by Italfarmaco S.p.A. ~~Drug Safety Manager, or Study Director,~~ or **their** ~~his~~ designee**(s)**.

The Investigator must notify the SAE to the **Drug Safety Unit (hereinafter "DSU") of** Italfarmaco S.p.A. ~~Drug Safety Unit (DSU)~~ by **sending** ~~faxing and/or mailing (only in case the mail will be automatically generated by the e-CRF)~~ the SAE **F**~~f~~orm**, according with the procedures indicated in the study manual and** within 24 hours of ~~a SAE, at the number specified below~~**learning of its occurrence.** ~~.; then, only in case the SAE will be faxed to the Italfarmaco S.p.A. DSU, the Investigator must confirm any SAE notifications by mailing to the mail address or phoning to the phone number specified below:~~**The details of the DSU are specified here below:**

PPD

Italfarmaco S.p.A.
Drug Safety Unit
~~Italfarmaco S.p.A.~~
Via dei Lavoratori, 54
20092 Cinisello Balsamo (MI), Italy
Phone: PPD
Fax: PPD
Fax (back-up):+PPD
Mobile: PPD
~~Fax:~~ PPD
e-mail: PPD

The same procedure must be applied to the SAE follow-up information.

All serious and unexpected AE that are associated with the use of the study drug (SUSARs) will be notified by Italfarmaco S.p.A. **DSU** ~~rug Safety Manager~~ to the competent authority within the required time and following procedures required by applicable laws. It is imperative that Italfarmaco S.p.A. be informed as soon as possible, so that reporting can be done within the required time frame.

The SAEs will also be recorded in the dedicated AE section of the CRF.

5.3.2 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 shall be immediately stopped. The investigator is required to report the pregnancy to Italfarmaco S.p.A. ~~Drug Safety Unit (~~**DSU**~~)~~ within 24 hours **of learning of its occurrence** via telephone and/or fax and/or mail (only in case the mail will be automatically generated by the e-CRF). If initially reported via telephone, this must be followed-up with a written report via fax and/or mail (only in case the mail will be automatically generated by the e-CRF) within 24 hours of the telephone report.

Patients should be 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 should be followed until termination, any premature termination should be reported, and the status of the mother and child should be reported to the sponsor after delivery.

If the Investigator is made aware that the partner of a male patient who is participating to the study become pregnant, he/she is required to report the pregnancy to Italfarmaco S.p.A. DSU within 24 hours via telephone and/or fax and/or mail (only in case the mail will be automatically generated by the e-CRF). If initially reported via telephone, this must be followed-up with a written report via fax and/or mail (only in case the mail will be automatically generated by the e-CRF) within 24 hours of the telephone report.

Whenever possible, such pregnancy should be followed until termination, any premature termination should be reported, and the status of the mother and child should be reported to the sponsor after delivery.

6.2 Statistical methods to be employed

Methods here represent the outline of the intended methods.

A Statistical Analysis Plan (SAP) will be produced before the database lock and will contain full details of all planned summaries, listings and analyses.

A standard 3+3 design adopting a modified Fibonacci escalation schema will be used in ***Part A*** [**25**, **26**, **27**].

Sample size for ***Part B*** was discussed for the primary end point defined as the Overall Response Rate after 3 cycles. Simon's 2-stage design will be employed in ***Part B*** [**30**] with the aim of testing the "null hypothesis" that RR ≤ 0.50 versus the "alternative" that RR ≥ 0.75. Response rate will be assessed as defined in paragraph 6.2.5.2. Overall up to 28 patients will need to be recruited, 12 patients being enrolled in Stage-1. PV patients enrolled at the MTD in ***Part A*** may be counted towards Stage 1. Under the "null hypothesis" (if RR = 0.50), the expected total sample size is of 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 favour 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 respond to the treatment the trial will be terminated rejecting the "alternative" that RR ≥ 0.75. Otherwise, the trial goes on to Stage-2 enrolling further 16 patients to a total of 28 patients. If at the end of Stage-2, a total of 17 or fewer patients respond to the treatment the "alternative hypothesis" that RR ≥ 0.75 will be rejected; alternatively, if 18 or more patients respond, the "null hypothesis" that RR ≤ 0.50 will be rejected. Estimations are obtained from proprietary software (based on SAS ® 9.2) according to the algorithm proposed by R. Simon [**30**].

Summary statistics will be calculated for all variables. For each continuous variable, the mean, standard deviation, median, minimum value and maximum value will be computed. For each discrete variable the number of patients in each category with non-missing values in relation to all patients with non-missing values of that variable will be provided. Results will be displayed within each cohort and overall, where applicable. Statistical calculations will be carried-out by resorting to SAS version 9.2 (or later). Both continuous and categorical data will be summarized and tabulated in 2-way tables (variable-by-visit). The main purpose of this phase Ib/II study consists in providing accurate estimates of clinically relevant variables and measures. From the statistical viewpoint this translates in estimating confidence intervals (CIs) with adequate precision where precision represents the degree of uncertainty.

The two tailed 95% CIs of the sample estimates will be computed using parametric approaches if deemed appropriate. Otherwise the StatXact-4 software will be used in order to compute Exact/Nonparametric 95% CIs.

Sub-groups analyses will be performed mainly for exploratory purposes. Since these analyses will be used to promote hypothesis 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.

6.2.1 Analysis Sets

The following analysis sets will be defined:

- Safety analysis set (SAF): The Safety analysis set will include all recruited patients who receive at least one dose of study medication. All safety analyses will be conducted on this population.
- 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. 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**.
- Per Protocol analysis set (PP): In order to assess the robustness of the efficacy analysis, the analysis of the efficacy end-point could be repeated in 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.
- MTD analysis set: 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.
- PK Analysis set: will consist of all SAF patients who with at least 1 PK assessment. This analysis set will be used for PK analysis.

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.

6.2.9 Interim analyses

Italfarmaco S.p.A. will perform a preliminary analysis of data after **the completion of the first cycle of treatment from all patients recruited in** *Part A*, in order to assess the MTD to be used for *Part B*.

Moreover, a preliminary analysis will be performed on the 12 patients of the first stage of Part B: if six or fewer responses will be observed during the first stage then the study will be stopped; 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. In this case, a final statistical analysis will be performed considering all patients enrolled in the two study phases.

In addition, Italfarmaco S.p.A. can perform a preliminary analysis of data in case of necessary safety and efficacy updates (e.g. to update regulatory documents and/or the drug safety profile, to revise the development program).

8.4 Auditing procedures

Italfarmaco S.p.A. reserves the right to conduct auditing activities at any/all participating centres and contracted a CRO **or their delegates** in order to verify compliance with Italfarmaco S.p.A. internal SOPs, CRO **and/or their delegates** SOPs, the principles of GCP and all applicable laws. A Regulatory Authority may also wish to conduct an inspection (during the study or even after its completion). If an inspection is requested by a Regulatory Authority, the Investigator must inform Italfarmaco S.p.A. immediately that this request has been made.

8.5 Handling of study medication

All study medication will be supplied to the pharmacy of the Centre by Italfarmaco S.p.A. or its designee. Drug supplies must be kept in an appropriate, secure area and stored in accordance with the conditions specified on the drug labels. The investigator must maintain an accurate record of the shipment and dispensing of the IMP in the drug accountability form. An accurate record of the date and amount of study drug dispensed to each patient must be available for inspection at any time. Copies of the drug accountability form will be provided to Italfarmaco S.p.A. by the investigator.

All drug supplies are to be used only for this protocol and not for any other purpose. The investigator must not destroy any partly-used or unused drug supply without authorization from Italfarmaco S.p.A.. At the conclusion of the study, and, as appropriate during the course of the study, the investigator will return all used and unused drug containers **to Italfarmaco S.p.A., Dipartimento di Tecnica Farmaceutica, Viale Fulvio Testi, 330, 20126 Milan (MI), Italy or their designee (e.g. CMO)**, and a copy of the completed IMP accountability form to the Italfarmaco S.p.A. monitor.

8.6 Ownership of data, disclosure and confidentiality

The investigator must assure that patients' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the sponsor,

patients should not be identified by their names, but by an identification code. The investigator should keep a**n** enrolment log showing codes, names and addresses.
By signing the protocol, the Investigator agrees to keep all information provided by Italfarmaco S.p.A. in strict confidence and to request similar confidentiality from his/her staff and the IRB/ECs. Study documents provided by Italfarmaco S.p.A. (protocols, investigators' brochures, CRFs and other material) will be stored appropriately to ensure their confidentiality. The information provided by Italfarmaco S.p.A. to the Investigator may not be disclosed to others without direct written authorization from Italfarmaco S.p.A., except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.
Italfarmaco S.p.A assures that the key design items of the Protocol will be published in a publicly accessible database such as "Clinicaltrials.gov". Moreover, upon completion of the Study and finalization of the Study report, the Results of these study will be submitted for publication or posted in a publicly accessible data base.
By signing the protocol, the investigators and their co-workers accept to submit any intended communication (abstract, paper or oral presentation) to Italfarmaco S.p.A. reasonably in advance (at least 30 working days for an abstract or oral presentation and 60 working days for a manuscript). This is to allow Italfarmaco S.p.A. to review the communications for accuracy and confidentiality, to provide any relevant supplementary information and to allow establishment of co authorship and in no way has to be intended as a restriction of the sponsor to the investigators' right to publish the results of the study. In case Italfarmaco S.p.A. identifies specific need/opportunity to patent any of the study findings, the Investigator will allow a six month time-window between his submission to Italfarmaco S.p.A. and the intended publication and actual submission/communication to third parties, in order to allow Italfarmaco S.p.A. to undertake appropriate patenting steps.

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10.1.1.1 Flow-chart of Cycle 1

Cycle Description	Screening	Cycle 1										
Cycle Day	-28 to Day -1	Day 1		Day 2	Day 3	Day 4	Day 8	Day 10	Day 15	Day 22	Day 28	EOS[11]
Treatment phase	Pre-dose	Pre-dose	Post-dose	TREATMENT								
Window	± 7 days	Not applicable					± 3 days					
Visit at the investigational site	X	X	X	X	X	X	X	X	X	X	X	X
Informed Consent Form signature	X											
Demographic data	X											
Adverse event recording	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications (drugs)	X	X	X	X	X	X	X	X	X	X	X	X
Non-drug therapies (e.g. phlebotomies, transfusions)	X	X	X	X	X	X	X	X	X	X	X	X
Medical history	X											
Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), height, weight, body temperature and ECOG performance status[1]	X			X			X		X	X	X	X
Physical examination, weight, body temperature and ECOG performance status		X										
Vital signs (blood pressure, pulse rate, respiratory rate)		X										
Vital signs (blood pressure, pulse rate, respiratory rate) *4 hours after the first Givinostat dose*			X									

Cycle Description	Screening	Cycle 1										
Cycle Day	-28 to Day -1	Day 1		Day 2	Day 3	Day 4	Day 8	Day 10	Day 15	Day 22	Day 28	EOS[11]
Treatment phase	Pre-dose	Pre-dose	Post-dose	TREATMENT								
Window	± 7 days	Not applicable					± 3 days					
Visit at the investigational site	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (*if indicated*)[2]	X											
Blood chemistry[3]	X	X					X		X	X	X	X
ECG, QTc determination (according with Bazett's correction formula) *3 hours after the first Givinostat dose*[12]	~~X~~	~~X~~	X	~~X~~			~~X~~		~~X~~	~~X~~	~~X~~	~~X~~
ECG, QTc determination (according with Bazett's correction formula)[12]	**X**	**X**		**X**			**X**		**X**	**X**	**X**	**X**
Urinalysis[4]	X										X	X
Haematology[5]	X						X		X	X	X	X
PD sample collection*		X										
PD sample collection *12 hours after the first Givinostat dose* *			X									
PK sample collection **and preparation, in order to allow to perform both the PK and PD evaluations starting from the same sample**[6,*]		X	X								X	
Spleen evaluation (by MRI or CT scan)[7]	X											X
Therapeutic response evaluation [8]												X
Collection of a blood sample for the quantitative RT-PCR evaluation of $JAK2^{V617F}$ mutational status on peripheral blood (PB) granulocyte*	X											

Cycle Description	Screening	Cycle 1										
Cycle Day	-28 to Day -1	Day 1		Day 2	Day 3	Day 4	Day 8	Day 10	Day 15	Day 22	Day 28	EOS[11]
Treatment phase	Pre-dose	Pre-dose	Post-dose	TREATMENT								
Window	± 7 days	Not applicable					± 3 days					
Visit at the investigational site	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of disease-related symptoms using the MPN-SAF QOL Questionnaire	X											X
Request of enrolment and receipt of patient ID	X											
First Givinostat dose and accountability			X									
Givinostat administration **and accountability**[9]				X	X	X	X	X	X	X	X	
Used/unused/partially used Givinostat supply return from patient(s) and Givinostat accountability[10]				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

[1] *Height* will be measured at the pre-treatment evaluations only.
Patients must have an ECOG ≤ 1 within 7 days of initiating study drug.

[2] *Pregnancy test* has to be 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 must be confirmed with a serum pregnancy test.

[3] *Blood Chemistry*: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN **or Urea** (**according with the site-specific clinical practice**), glucose, Na, K, Ca, Cl, Mg, albumin**, eGFR determination (according with the Mayo Clinic Quadratic Equation)**.

[4] *Urinalysis*: pH, specific gravity, protein, glucose.

[5] *Haematology*: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count.

[6] *PK sample collection*: as following summarize:
- Day 1: pre-dose and 2, 3 and 8 hours post-dose;
- Day 28: pre-dose and 1, 2, 4 and 8 hours post-dose.

Patients will not take the morning dose of Givinostat on the day selected for their timed PK assessments. Study drug will be 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 will take the morning dose of study drug prior to the visit.

[7] *Spleen evaluation as per site-specific clinical practise*: Patients with splenomegaly will be followed according to institutional guidelines (i.e. MRI or CT scan). The same imaging technique and the same instrument should be used on a patient throughout the study, if possible. **No spleen evaluation will be performed in splenectomised patients.**

[8] *Therapeutic response evaluation*: for PV and ET (*if any*), according with the clinico-haematological ELN response criteria [21] (see paragraph 4.6.1); for MF (*if any*), according with EUMNET response criteria.

[9] *Givinostat administration*: patients can take drug at home, except for the first drug administration.

[10] *IMP*: at study close-out, and as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and the completed drug forms to Italfarmaco S.p.A., Dipartimento di Tecnica Farmaceutica, Viale Fulvio Testi, 330, 20126, Milan **(MI)**, Italy **or their designee (e.g. CMO)**.

Only in some particular cases, after the authorization of Italfarmaco S.p.A. (or after a signed agreement between the investigational site and Italfarmaco S.p.A.), these materials can be destroyed locally.

[11] *EOS:* In case of the patient drops-out of the study, the end of Study (EOS) visit will be performed 7 days after last drug intake.

Note that, as reported in the paragraph 4.3.3, if the patient discontinues for any reason (including discontinuation for pregnancy), with drug related adverse event ongoing at study end, he/she must be followed until resolution or stabilization of the event or until it is 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 events" should be indicated as the primary reason whenever applicable. All relevant information related to the reason for treatment discontinuation including contributory factors must be included on the 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. Should any drug-related AE still be ongoing beyond the last scheduled visit, this must be followed at subsequent follow-up visits until recovery. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance every effort should 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 must be included on the CRF.

[12] ***ECG*: If the ECG evaluation demonstrates 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) must be performed. The averaged value of these three ECG evaluations has to be used for the evaluation of the QTc interval. In the CRF all the performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*.**

[*] For all time points a blood sample will be collected as back-up sample.

10.1.1.2 Flow-chart of Cycle 2 and beyond

	Day 1 of each cycle	Day 28 of cycles 2, 4 and 5	Day 28 of cycles 3 and 6	End of study visit (in case of completed study) or 7 days after last drug intake (in case of the patient drops-out of the study)[8]
Treatment phase	TREATMENT			
Window	± 3 days			
Visit at the investigational site		X	X	X
Adverse event recording		X	X	X
Concomitant medications (drugs)		X	X	X
Non-drug therapies (e.g. phlebotomies, transfusions)		X	X	X
Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status		X	X	X
Blood chemistry[1]		X	X	X
ECG, QTc determination (according with Bazett's correction formula)[9]		X	X	X
Haematology[2]		X	X	X
PK sample collection and preparation, in order to allow to perform both the PK and PD evaluations starting from the same sample [3, *]		X	X	
Spleen evaluation (by MRI or CT scan)[4]			X	X
Therapeutic response evaluation[5]			X	X
Collection of a blood sample for the quantitative RT-PCR evaluation of $JAK2^{V617F}$ mutational status on peripheral blood (PB) granulocyte[*]			X	X
Assessment of disease-related symptoms using the MPN-SAF QOL Questionnaire			X	X
Givinostat administration[6]	X	X	X[10]	
First Givinostat dose of the related cycle and accountability	X			

	Day 1 of each cycle	Day 28 of cycles 2, 4 and 5	Day 28 of cycles 3 and 6	End of study visit (in case of completed study) or 7 days after last drug intake (in case of the patient drops-out of the study)8
Treatment phase	TREATMENT			
Window	± 3 days			
Visit at the investigational site		X	X	X
Used/unused/partially used Givinostat supply return from patient(s) and accountability[7]		X	X	X

[1] *Blood Chemistry*: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN **or Urea (according with the site-specific clinical practice)**, glucose, Na, K, Ca, Cl, Mg, albumin**, eGFR determination (according with the Mayo Clinic Quadratic Equation)**.

[2] *Haematology*: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count.

[3] *PK sample collection:* pre-dose. **Patients will not take the morning dose of Givinostat on the day selected for their timed PK assessments. Study drug will be 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 will take the morning dose of study drug prior to the visit.**

[4] *Spleen evaluation as per site-specific clinical practise*: Patients with splenomegaly will be followed according to institutional guidelines (i.e. MRI or CT scan). The same imaging technique and the same instrument should be used on a patient throughout the study, if possible. **No spleen evaluation will be performed in splenectomised patients.**

[5] *Therapeutic response evaluation*: for PV and ET (*if any*), according with the clinico-haematological ELN criteria [21] (see paragraph 4.6.1); for MF (*if any*), according with EUMNET response criteria.

[6] *Givinostat administration*: patients can take drug at home.

[7] *IMP*: at study close-out, and as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and the completed drug forms to Italfarmaco S.p.A., Dipartimento di Tecnica Farmaceutica, Viale Fulvio Testi, 330, 20126, Milan **(MI)**, Italy **or their designee (e.g. CMO)**. Only in some particular cases, after the authorization of Italfarmaco S.p.A. (or after a signed agreement between the investigational site and Italfarmaco S.p.A.), these materials can be destroyed locally.

[8] ***EOS:*** **as reported in the paragraph 4.3.3, if the patient discontinues for any reason (including discontinuation for pregnancy), with drug related adverse event ongoing at study end, he/she must be followed until resolution or stabilization of the event or until it is reasonable to consider the event not drug related any more or until the start of a new treatment, whichever occurs first.**

Amendment 2
Version 1.0 – 29th July 2015

In case of multiple reasons (e.g. patient withdraws the consent for toxicity), "adverse events" should be indicated as the primary reason whenever applicable. All relevant information related to the reason for treatment discontinuation including contributory factors must be included on the 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. Should any drug-related AE still be ongoing beyond the last scheduled visit, this must be followed at subsequent follow-up visits until recovery. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance every effort should 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 must be included on the CRF.
Of note, 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 the Cycle 6 Day 28 visit can be counted for the End of Study visit.

In addition, in case the patient completes the study (i.e. performs all the evaluations requested to be done at the Day 28 of Cycle 6) and she/he is eligible to continue the study drug treatment in the long-term study (i.e. Study DSC/11/2357/44), the evaluation performed at the Cycle 6 Day 28 visit of this study can be also counted for the pre-treatment evaluations of the Study DSC/11/2357/44, provided that no difference in the evaluation is present between the two studies (e.g. haematological and biochemical evaluations). No additional Givinostat study (i.e. Study DSC/12/2357/45)-specific assumption has to be done at the completion of the Day 28 of Cycle 6. Indeed, in case the patient completes the study (i.e. performs all the evaluations requested to be done at the Day 28 of Cycle 6 of this study), she/he is eligible to continue the study drug treatment in the long-term study (i.e. Study DSC/11/2357/44) and she/he receive the written authorization of the treatment from the Sponsor of their designee (i.e. a patient's confirmation form that includes the patient ID to use into the Study DSC/11/2357/44), the patient will continue the study drug treatment into the Study DSC/11/2357/44, receiving the study (i.e. Study DSC/11/2357/44)-specific drug to be taken.

[9] ***ECG*: If the ECG evaluation demonstrates 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) must be performed. The averaged value of these three ECG evaluations has to be used for the evaluation of the QTc interval. In the CRF all the performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*.**

[10] ***Givinostat administration*: Only for *cycle 3*.**

[*] For all time points a blood sample will be collected as back-up sample.

10.1.2 Flow-chart of *Part B*

	Pre-treatment evaluations*** (up to 4 weeks: -28 to Day -1)	Day 1 of the first Cycle***		Day 28 of Cycles 1, 2, 4 and 5***	Day 28 of Cycles 3 and 6***	End of study visit (in case of completed study) or 7 days after last drug intake (in case of the patient drops-out of the study)[11, ***]
Treatment phase	Pre-dose	Pre-dose	Post-dose	TREATMENT		
Windows	± 7 days	Not applicable		± 3 days		
Visit at the investigational site	X	X	X	X	X	X
Informed Consent Form signature	X					
Demographic data	X					
Adverse event recording	X	X	X	X	X	X
Concomitant medications (drugs)	X	X	X	X	X	X
Non-drug therapies (e.g. phlebotomies, transfusions)	X	X	X	X	X	X
Medical history	X					
Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), height, weight, body temperature and ECOG performance status[1]	X			X	X	X
Pregnancy test (*if indicated*) [2]	X					
Blood chemistry[3]	X			X	X	X
ECG, QTc determination (according with Bazett's correction formula)[12]	X			X	X	X
Urinalysis[4]	X					
Haematology[5]	X			X	X	X
PD sample collection before the first Givinostat dose*		X				
PD sample collection 12 hours after the first Givinostat dose *			X			
PK sample collection[6, *] **and preparation, in order to allow to perform both the PK and PD evaluations starting from the same sample (*if requested*)**		X	X	X		

	Pre-treatment evaluations (up to 4 weeks: -28 to Day -1)***	Day 1 of the first Cycle***		Day 28 of Cycles 1, 2, 4 and 5	Day 28 of Cycles 3 and 6	End of study visit (in case of completed study) or 7 days after last drug intake (in case of the patient drops-out of the study)[11]
Treatment phase	Pre-dose	Pre-dose	Post-dose	TREATMENT		
Windows	± 7 days	Not applicable		± 3 days		
Visit at the investigational site	X	X	X	X	X	X
Spleen evaluation (by MRI or CT scan)[7]	X				X	X
Collection of blood sample for quantitative RT-PCR evaluation of $JAK2^{V617F}$ mutational status on peripheral blood (PB) granulocyte *	X			**X**	X	X
Assessment of disease-related symptoms using the MPN-SAF QOL Questionnaire [24, 32]	X				X	X
Bone marrow histological evaluation in order to assess the presence of age adjusted normocellularity and/or trilinear hyperplasia[A]	X				X^{B}	X^{C}
Therapeutic response evaluation[8]					X	X
Request of enrolment and receipt of patient ID	X					
Givinostat administration[9]				X	X**	
First Givinostat dose and accountability			X			
Used/unused/partially used Givinostat **supply** return from patient(s) and accountability[10]				X	X	X

[1] *Height* will be measured at the pre-treatment evaluations only.
Patients must have an ECOG ≤ 2, within 7 days of initiating study drug.

[2] *Pregnancy test* has to be performed within 72 hours before the first Givinostat dose. The test can be performed by urine or serum pregnancy test. In case of a positive or borderline-positive urine pregnancy test, this must be confirmed with a serum pregnancy test.

[3] *Blood Chemistry*: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN **or Urea (according with the site-specific clinical practice)**, glucose, Na, K, Ca, Cl, Mg, albumin**, eGFR determination (according with the Mayo Clinic Quadratic Equation).**

[4] *Urinalysis*: pH, specific gravity, protein, glucose.

[5] *Haematology*: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count.

[6] *PK sample collection*: as following summarize:

- Day 1 of Cycle 1: pre-dose and 2, 3 and 8 hours post-dose;
- Day 28 only of Cycle 2: pre-dose and 1, 2, 4 and 8 hours post-dose.

Patients will not take the morning dose of Givinostat on the day selected for their timed PK assessments. Study drug will be 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 will take the morning dose of study drug prior to the visit.

[7] *Spleen evaluation as per site-specific clinical practise*: ~~Patient with splenomegaly~~**The spleen evaluation** will **be performed during the study** ~~followed~~ according to institutional guidelines **and site-specific clinical practice** (i.e. MRI or CT scan). The same imaging technique and the same instrument should be used on a patient throughout the study, *if possible*. **No spleen evaluation will be performed in splenectomised patients.**

[8] *Therapeutic response evaluation*: both according with the clinico-haematological ELN criteria [21] (see paragraph 4.6.1) (*both at cycle 3 and at cycle 6*) and according with the "new" ELN criteria (i.e. revised ELN response criteria) [33] (see paragraph 4.8.7) (*only at cycle 6)*.

[9] *Givinostat administration*: patients can take drug at home, except for the first drug administration.

[10] *IMP*: at study close-out, and as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and the completed drug forms to Italfarmaco S.p.A.**,** ―Dipartimento di Tecnica Farmaceutica**,** Viale Fulvio Testi, 330, 20126~~,~~ Milan **(MI)**, Italy **or their designee (e.g. CMO)**.

Only in some particular cases, after the authorization of Italfarmaco S.p.A. (or after a signed agreement between the investigational site and Italfarmaco S.p.A.), these materials can be destroyed locally.

[11] ***EOS:*** **as reported in the paragraph 4.3.3, if the patient discontinues for any reason (including discontinuation for pregnancy), with drug related adverse event ongoing at study end, he/she must be followed until resolution or stabilization of the event or until it is 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 events" should be indicated as the primary reason whenever applicable. All relevant information related to the reason for treatment discontinuation including contributory factors must be included on the 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. Should any drug-related AE still be ongoing beyond the last scheduled visit, this must be followed at subsequent follow-up visits until recovery. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance every effort should 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 must be included on the CRF.

Of note, 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 the Cycle 6 Day 28 visit can be counted for the End of Study visit.

In addition, in case the patient completes the study (i.e. performs all the evaluations requested to be done at the Day 28 of Cycle 6) and she/he is eligible to continue the study drug treatment in the long-term study (i.e. Study DSC/11/2357/44), the evaluation performed at the Cycle 6 Day 28 visit of this study can be also counted for the pre-treatment evaluations of the Study DSC/11/2357/44, provided that no difference in the evaluation is present between the two studies (e.g. haematological and biochemical evaluations). No additional Givinostat study (i.e. Study DSC/12/2357/45)-specific assumption has to be done at the completion of the Day 28 of Cycle 6. Indeed, in case the patient completes the study (i.e. performs all the evaluations requested to be done at the Day 28 of Cycle 6 of this study), she/he is eligible to continue the study drug treatment in the long-term study (i.e. Study DSC/11/2357/44) and she/he receive the written authorization of the treatment from the Sponsor of their designee (i.e. a patient's confirmation form that includes the patient ID to use into the Study DSC/11/2357/44), the patient will continue the study drug treatment into the Study DSC/11/2357/44, receiving the study (i.e. Study DSC/11/2357/44)-specific drug to be taken.

[12] ***ECG*: If the ECG evaluation demonstrates 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) must be performed. The averaged value of these three ECG evaluations has to be used for the evaluation of the QTc interval. In the CRF all the performed ECG evaluations have to be entered as well as the average value of multiple ECG evaluation, *if necessary*.**

[*] For all time points a blood sample will be collected as back-up sample.

[**] Only for *cycle 3*.

[***] **Patients should be told to arrive after an overnight fast of at least 8 hours at all study visits that request a blood test. However, the study visits should still be conducted even if the patient does not adhere to fasting requirements and this will not be considered a protocol violation. In these cases, this information (i.e. not fasting condition) has to be noted by the Investigator in the medical chart and reported in CRF, in order to avoid any misunderstanding of the collected data (e.g. glucose value is influenced by fasting/not fasting conditions).**

[A] Please note that, in case the patient performs the bone marrow histological evaluation as requested by the "new" ELN criteria (i.e. the revised ELN response criteria) [33] (see paragraph 4.8.7) – 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 Informed Consent Form), 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 will be transcribed into the 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, will be monitored and stored at the study site.

Finally, in case the patient refuses to provide this written consent to perform the bone marrow evaluation, this patient can be anyway 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 [33], and the evaluation of the effect of Givinostat on each single response parameter according to the revised ELN response criteria [33]).

[B] Only for *cycle 6*.

[C] In case the patient drops-out the study during the first 3 Cycles (i.e. before the Day 28 of Cycle 3) , this evaluation has not to be performed at End of Study visit.

10.5 Appendix E: $JAK2^{V617F}$ genotyping and quantification in granulocytes

$JAK2^{V617F}$ genotyping and quantification will be performed **in *Part A* at the screening, at** ~~during the pre-treatment evaluations,~~ **Day 28 of Cycle 3, at Day 28 of Cycle 6 and at the end of study, and in *Part B* at the screening, at Day 28 of each Cycle (i.e. Day 28 of the Cycles 1, 2, 3, 4, 5 and 6)and at the end of study** ~~at the end of every year of treatment and at the end of the study (in case of completed study) or 7 days after last drug intake (in case of the patient drops-out of the study)~~. A sample of peripheral blood in EDTA (20 mL) will be obtained, and either granulocyte are separated in the same institution up to the freezing of a granulocyte pellet, or the blood sample is sent the same day with an O/N courier to the Central Laboratory. Granulocytes are prepared from peripheral blood (PB) samples using density-gradient centrifugation and residual erythrocyte lyses; granulocytes are frozen as a pellet. Frozen pellets from different patients can be sent in blocks to the Central Laboratory in dry ice. DNA is extracted using solid-phase extraction. The presence and the mutation, and the allelic burden, are evaluated in triplicate in each sample, using a quantitative real-time PCR (RT-PCR) technique and standard curve with plasmids available the Central Laboratory [31].

STUDY N.: DSC/12/2357/45

EUDRACT N.: 2013-000860-27

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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AMENDMENT 1 RATIONALE

The clinical study protocol DSC/12/2357/45 has been amended for the following reasons:

- To clarify the meaning of an "*effective* means of contraception for women of childbearing potential and men with partners of childbearing potential" (i.e. inclusion criteria n. 5) mentioning that the contraceptive methods will be used for up to 3 months after stopping the study treatment, as requested by French Regulatory Authority;
- To update the patient numbering sections as per eCRF;
- To add as 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, 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).

Further to what is reported above, with the present amendment some typographic mistakes existing in the clinical study protocol version 1.0 (dated 01st March 2013) have been put right.

AMENDMENT 1 SUMMARY OF CHANGES

Substantive additions to the protocol are denoted in **bold**. Substantive deletions are in ~~strikethrough~~.

2.1 Primary Objectives

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 [21] (see paragraph 4.6.1)**.
- 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 [21] (see paragraph 4.6.1)**.
- 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 [21] (see paragraph 4.6.1)**.
- To determine the safety and tolerability of Givinostat at the MTD after 6 cycles.
- To characterize PK.

2.3 Exploratory Objectives

Parts A and B

- To evaluate the effect of Givinostat on single parameters of the **clinico-haematological ELN** response criteria **[21] (see paragraph 4.6.1)**.
- 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) [33] (see paragraph 4.8.7).**
- **To evaluate the effect of Givinostat on sigle parameters of the "new" ELN response criteria (i.e. the revised ELN response criteria) [33] (see paragraph 4.8.7).**

3.1 Primary endpoints

Part A

- Safety and tolerability evaluated as following:
  - 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).
- Determination of the MTD of Givinostat based on cycle 1 DLT's.

Part B

- Overall response rate - i.e. Complete Response (CR) and Partial Response (PR) - of Givinostat at the MTD after 3 cycles; the response will be evaluated according to the clinico-haematological ~~European LeukemiaNet (~~ELN~~)~~ response criteria [**21**] (see paragraph 4.6.1).
- Safety and tolerability of Givinostat at the MTD after 3 cycles evaluated as following:
  - Number of patients experiencing adverse events;
  - Type, incidence, and severity of treatment-related adverse events, graded according to CTCAE v. 4.03.

3.2 Secondary endpoints

Part A

- Overall response rate - i.e. Complete Response (CR) and Partial Response (PR) - of Givinostat at the MTD after 3 and 6 cycles; the response will be evaluated according to the **clinico-haematological** ELN response criteria [**21**] **(see paragraph 4.6.1)**.
- Individual Givinostat concentrations tabulated by dose cohort along with descriptive statistics.

Part B

- Overall response rate - i.e. Complete Response (CR) and Partial Response (PR) - of Givinostat at the MTD after 6 cycles; the response will be evaluated according to the clinico-haematological ELN response criteria [21] (see paragraph 4.6.1).
- Safety and tolerability of Givinostat at the MTD after 6 cycles evaluated as following:
  - Number of patients experiencing adverse events;
  - Type, incidence, and severity of treatment-related adverse events, graded according to CTCAE v. 4.03.
- Individual Givinostat concentrations tabulated with descriptive statistics.

3.3 Exploratory endpoints

Part A and Part B

- To evaluate the effect of Givinostat on each single response parameter according to the **clinico-haematological** ELN response criteria [21] **(see paragraph 4.6.1)**.
- To evaluate the effects of Givinostat on PD markers by mRNA analysis.
- To evaluate the effects of Givinostat on spleen size (by MRI or CT scan) in patients with confirmed splenomegaly at baseline.

- Improvement of constitutional symptoms evaluated according to MPN-SAF QOL questionnaire [**24, 32**].
- Reduction of the $JAK2^{V617F}$ allele burden, tested by quantitative RT-PCR.
- Reduction of the symptomatic treatment of pruritus in term of dosage and/or days of treatment.

Part B

- **Overall response rate - i.e. Complete Remission and Partial Remission - of Givinostat at the MTD after 6 cycles; the response will be evaluated according to the "new" ELN response criteria (i.e. the revised ELN response criteria [33], see paragraph 4.8.7).**
- **To evaluate the effect of Givinostat on each single response parameter according to the "new" ELN response criteria (i.e. the revised ELN response criteria [33], see paragraph 4.8.7).**

4.1 Overall study design

This is a two-part, multicenter, open label, non-randomized, phase Ib/II study to assess the safety and tolerability, MTD and preliminary efficacy of Givinostat in patients with JAK2V617F positive PV.

Part A is the dose escalation portion of the study and, once the MTD has been established, Part B will commence where the preliminary efficacy of Givinostat in PV patients will be established. Patients will be 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) may be counted towards the efficacy assessment in Part B.

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

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

Disease response will be evaluated according to the **clinico-haematological** ELN criteria [21] 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 will not be 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 will be allowed to continue treatment with Givinostat (at the same dose and schedule) in a long-term study (Study N.: DSC/11/2357/44).

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

4.1.1.5 Definition of MTD

If 2 or more patients per dose level experience a DLT, dose escalation will terminate and the MTD is the next lower dose level if no more than one out of 6 patients had a DLT at that level. Once all patients enrolled in Part A have been treated for at least 1 cycle, the study team will 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 will be permitted prior to determining the MTD. At that time, continuing patients at lower dose levels may be allowed to escalate their Givinostat dose to the MTD **for** the remainder **part** of the study (Part **A~~B~~**) at the discretion of the Investigator and Sponsor.

4.3.1 Inclusion criteria

Patients must meet the following criteria to be eligible for study entry:

1. Patients must be able to provide informed consent through the signature of an informed consent form;
2. Patients must have an age ≥18 years;
3. Patients must have a confirmed diagnosis of PV according to the revised WHO criteria;
4. Patients must have $JAK2^{V617F}$ positive disease;
5. Patients must have an active/not controlled disease defined as
   a) HCT ≥ 45% or HCT <45% in need of phlebotomy, and
   b) PLT counts > 400 $x10^9$/L, and

c) WBC > 10 x10^9/L;

6. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status [28] ≤ 1 in Part A, ECOG performance status ≤ 2 in Part B, within 7 days of initiating study drug;
7. Female patient of childbearing potential has a negative serum or urine pregnancy test within 72 hours of the first dose of study therapy; please note that a borderline urine pregnancy test must be followed with a serum pregnancy test;
8. Use of an effective means of contraception for women of childbearing potential and men with partners of childbearing potential;
9. Adequate and acceptable organ function within 7 days of initiating study drug;
10. Willingness and capability to comply with the requirements of the study.

Note that if the enrolment in Part A is slow (i.e. < 5 patients enrolled in 3 months), eligibility for this part of the study may be expanded to all patients with cMPN. In this case, the inclusion criteria 5 will be modified as following only for Part A:

5. Patients must have an active/not controlled disease defined as:

a) ET patients: PLT counts > 600 x10^9/L;

b) MF patients: no response according to EUMNET criteria [29].

Note that an effective means of contraception for women of childbearing potential and men with partners of childbearing potential (i.e. inclusion criteria n. 5) is defined as following described based on different subject subgroups:

A. Female subjects of childbearing potential: acceptable non-hormonal, contraceptive methods must be used from the 28 days before first dose of study drug through 3 months after the last dose of study drug and include the following:

- **True abstinence (absence of any sexual intercourse), when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.**
- **Double barrier contraception such as diaphragm or a barrier method of contraception in conjunction with spermicidal jelly such as for example cervical cap with spermicide jelly and the male partner must use a condom with spermicide.**
- **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 a negative sperm post-vasectomy semen analysis) at least 6 months previously and 1 additional acceptable contraception method.**

B. Female subjects of non-childbearing potential must meet at least 1 of the following criteria:

- **Postmenopausal: Female subjects, less than 60 years of age, who have been amenorrheic for at least 2 years and have a serum FSH level within the laboratory's reference range for postmenopausal females. Female subject who are 60 years of age or older who are amenorrheic for greater than 2 years will be assume to be postmenopausal.**
- **Documented hysterectomy or bilateral oophorectomy or both All other female subjects (including subjects with tubal ligations and subjects that do not have a documented hysterectomy) will be considered to be of childbearing potential.**

C. Male Subjects, acceptable contraceptive methods must be used from Screening Visit through 3 months after the last dose of study drug, and include the following:

- **True abstinence (absence of any sexual intercourse), when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.**
- **Condom with spermicide and the female partner must use an acceptable method of contraception, such as an oral, transdermal, injectable or implanted steroid-based contraceptive, or a diaphragm or a barrier method of contraception in conjunction with spermicidal jelly such as for example cervical cap with spermicide jelly.**
- **Vasectomy (with a negative sperm post-vasectomy semen analysis) at least 6 months previously and 1 additional acceptable contraception method**
- **Male subjects must not donate sperm from the Screening Visit through 3 months after the last dose of study drug**

Note also that

- **Male condom cannot be used with female condom due to risk of tearing.**
- **The use of birth-control methods does not apply if the female partner has a bilateral oophorectomy, hysterectomy, or is postmenopausal (as defined above).**

4.3.3 Criteria for dose modifications

...

In case of multiple reasons (~~i.~~**e.g.** patient withdraws the consent for toxicity), "adverse events" should be indicated as the primary reason whenever applicable. All relevant information related to the reason for treatment discontinuation including contributory factors must be included on the CRF.

...

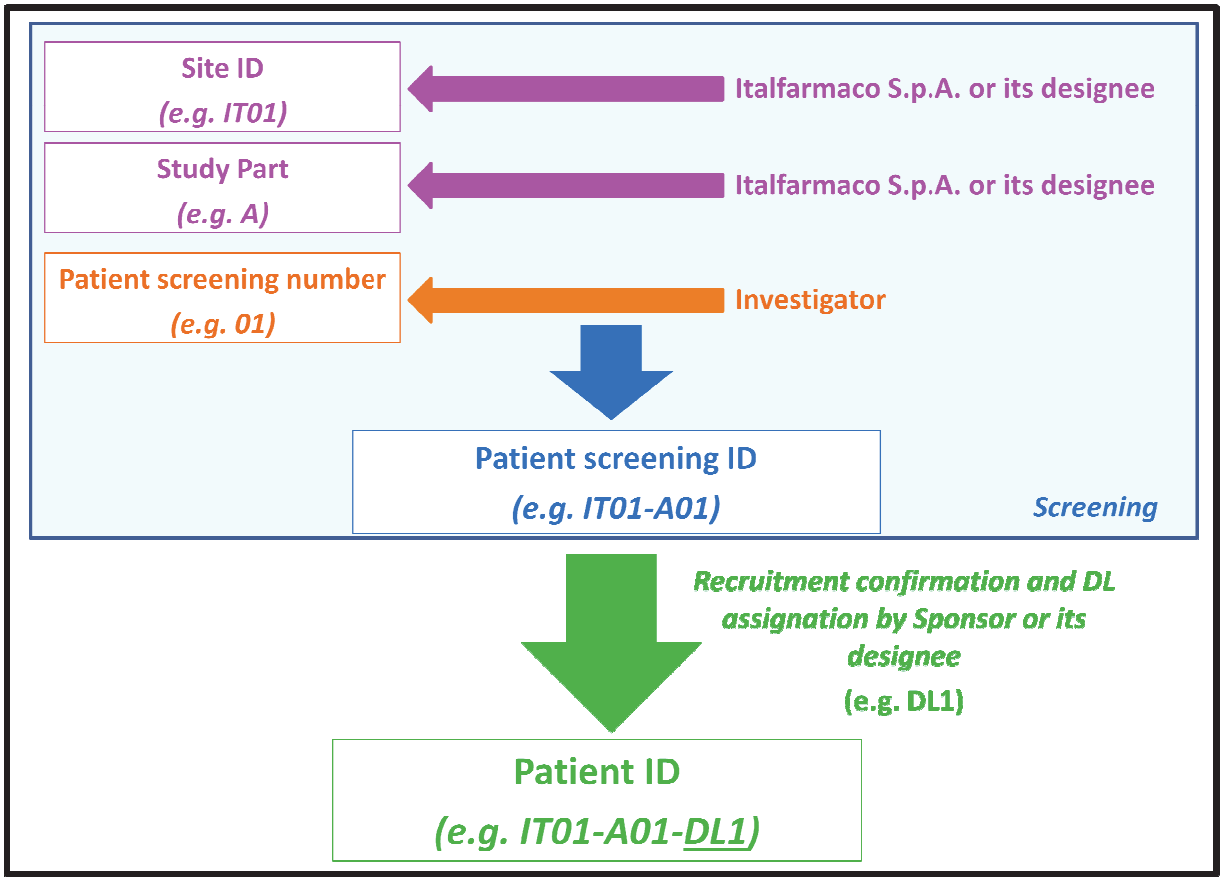
4.4.3 Patient numbering and screening

Each patient will be identified in the study by a patient **code** ~~ID which will be a combination of his/her site ID and patient number~~.

During the screening period (i.e. after the informed consent form signature and before the recruitment confirmation by the Italfarmaco S.p.A. or its designee), the patient code will be named patient screening ID and will be a combination of his/her site ID, study part ID and patient screening number.

Both t~~T~~he site ID **and the study part ID (i.e. "A" or "B" for *Part A* or *Part B*, respectively)** will be assigned by the Sponsor or its designee to the investigator site.

Upon signing the informed consent form, the patient **screening** number will be assigned by the Investigator. At each site, the first patient will be assigned patient number 1, and subsequent patients will be assigned consecutive numbers (e.g. the second patient will be assigned patient number 2, the third patient will be assigned patient number 3, etc).
When a study site has a patient ready to enrol, prior to dosing the site will compile a request for registration Form and send it to Italfarmaco S.p.A. or its designee in order to obtain the patient ID. The request for registration contains the site ID, **the study part ID,** the assigned patient **screening** number, a checklist related to the inclusion/exclusion criteria to verify the eligibility of the patient and collect some other information (e.g. date of birth, date of informed consent obtained). **If the patient is eligible, Italfarmaco S.p.A. or its designee will confirm the enrolment of the patient assigning the related dose level and the patient ID (i.e. the patient code after the enrolment confirmation) which will be a combination of patient screening ID and dose level ID.**
Once assigned, **both** the patient **screening ID and the patient ID**~~number~~ must not be reused for any other patient.
The following scheme will resume the patient identification process:



If the patient will fail to be enrolled for any reason, the reason will be entered in the study CRF within 2 days that the patient is not enrolled.
According to ICH-GCP guidelines, the Investigator will maintain a patient identification list, which ensures a distinctive identification of the patients by their name to screening numbers, date of birth, sex and date of inclusion.

4.5.3 Spleen evaluation, PK and PD characterization~~, and~~ molecular examinations **and bone marrow histological evaluation**

4.5.3.6 Bone marrow histological evaluation

A bone marrow histological evaluation will be performed to all patients recruited 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) [33] (see paragraph 4.8.7).

This examination will be performed in the local laboratory of each site. The results of this test will be transcribed into the 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, will be monitored and stored at the study site.
Please note that, in case the patient performs the bone marrow histological evaluation as requested by the "new" ELN criteria (i.e. the revised ELN response criteria) [33] (see paragraph 4.8.7) – 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 Informed Consent Form), 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 will be transcribed into the 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, will be monitored and stored at the study site.

In case the patient drops-out the study during the first 3 Cycles (i.e. before the Day 28 of Cycle 3), this evaluation has not to be performed at End of Study visit.

Finally, in case the patient refuses to provide this written consent to perform the bone marrow evaluation, this patient can be anyway 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 [33], and the evaluation of the effect of Givinostat on each single response parameter according to the revised ELN response criteria [33]).

4.5.4.1.2 Cycle 1

…

End of Study

In case of the patient drops-out of the study, the following procedures will be performed 7 days after last drug intake (within ± 3 days) as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (if applicable);
- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status;
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN (see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin;
- ECG, QTc determination (according with Bazett's correction formula);
- Urinalysis: pH, specific gravity, protein, glucose;
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- Spleen evaluation by MRI or CT scan;
- Therapeutic response evaluation **according to the clinico-haematological ELN response criteria [21] (see paragraph 4.6.1)**;
- Assessment of disease-related symptoms using the MPN-SAF QOL Questionnaire;
- Used/unused/partially used Givinostat supply return and accountability.

At study close-out, and as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and the completed drug forms to Italfarmaco S.p.A. – Dipartimento di Tecnica Farmaceutica Viale Fulvio Testi, 330, 20126, Milan, Italy.

Only in some particular cases, after the authorization of Italfarmaco S.p.A. (or after a signed agreement between the investigational site and Italfarmaco S.p.A.), these materials can be destroyed locally.

4.5.4.1.3 Cycles 2, 3, 4, 5 and 6

…

Day 28 of Cycles 3 and 6

The following procedures will be performed at Day 28 of Cycles 3 and 6 of Part A (within ± 3 days) as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (if applicable);
- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status;
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN (see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin;
- ECG, QTc determination (according with Bazett's correction formula);
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- PK sample collection (pre-dose);
- Spleen evaluation by MRI or CT scan;
- Therapeutic response evaluation **according to the clinico-haematological ELN response criteria [21] (see paragraph 4.6.1)**;
- Collection of a blood sample for the quantitative RT-PCR evaluation of $JAK2^{V617F}$ mutational status on peripheral blood (PB) granulocyte;
- Assessment of disease-related symptoms using the MPN-SAF QOL Questionnaire;
- Givinostat administration and accountability.

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 [21] (see paragraph 4.6.1)**.

End of Study

The following procedures will be performed at the end of study visit (in case of completed study) or 7 days after last drug intake (in case of the patient drops-out of the study) (within ± 3 days) as reported below:

- Adverse event recording;

- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (if applicable);
- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status;
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN (see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin;
- ECG, QTc determination (according with Bazett's correction formula);
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- Spleen evaluation by MRI or CT scan;
- Therapeutic response evaluation **according to the clinico-haematological ELN response criteria [21] (see paragraph 4.6.1)**;
- Collection of a blood sample for the quantitative RT-PCR evaluation of $JAK2^{V617F}$ mutational status on peripheral blood (PB) granulocyte;
- Assessment of disease-related symptoms using the MPN-SAF QOL Questionnaire;
- Used/unused/partially used Givinostat supply return and accountability.

At study close-out, and as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and the completed drug forms to Italfarmaco S.p.A. – Dipartimento di Tecnica Farmaceutica Viale Fulvio Testi, 330, 20126, Milan, Italy.

Only in some particular cases, after the authorization of Italfarmaco S.p.A. (or after a signed agreement between the investigational site and Italfarmaco S.p.A.), these materials can be destroyed locally.

4.5.4.2.1 Pre-treatment evaluations (up to 4 weeks: -28 to Day -1)

The following procedures will be performed at the pre-treatment visit of Part B as reported below:

- Informed consent signing;
- Demographic data (race, sex and date of birth);
- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (if applicable);
- Medical history;
- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), height, weight, body temperature and ECOG performance status;
- Pregnancy test (if indicated);

- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN (see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin;
- ECG, QTc determination (according with Bazett's correction formula);
- Urinalysis: pH, specific gravity, protein, glucose;
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- Spleen evaluation by MRI or CT scan;
- Collection of a blood sample for the quantitative RT-PCR evaluation of $JAK2^{V617F}$ mutational status on peripheral blood (PB) granulocyte;
- Assessment of disease-related symptoms using the MPN-SAF QOL Questionnaire **[24, 32]**;
- **Bone marrow histological evaluation, in patients who have consented to this optional exploratory research, who haven't this assessment in the month before the 1 month before the study start (i.e the signature of the Informed Consent Form, and that have not any medical contraindication to bone marrow sampling as judged by the Investigator;**
- Request of enrolment and receipt of patient ID.

The pregnancy test (if indicated) has to be 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 must be confirmed with a serum pregnancy test and the result recorded in the CRF.
Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status [28] ≤ 2 within 7 days of initiating study drug.
Patients with splenomegaly will perform the spleen evaluation as per site-specific clinical practice. Therefore, patients with splenomegaly before the treatment start will be followed according to institutional guidelines (i.e. MRI or CT scan). The same imaging technique and the same instrument should be used on a patient throughout the study, if possible.
Pre-treatment evaluations will be performed at one or more clinic visit to determine eligibility for the study. Pre-treatment evaluations must be performed up to 4 weeks before the treatment start within ± 7 days. **Please note that, in case the patient performs the bone marrow histological evaluation as requested by the "new" ELN criteria (i.e. the revised ELN response criteria) [33] (see paragraph 4.8.7) – 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 Informed Consent Form), 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 will be transcribed into the 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, will be monitored and stored at the study site.
In case the patient refuses to provide this written consent to perform the bone marrow evaluation, this patient can be anyway 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 [33], and the evaluation of the effect of Givinostat on each single response parameter according to the revised ELN response criteria [33]).
If all eligibility criteria are met at the pre-treatment visit, the treatment with Givinostat can start.
After the check that all eligibility criteria are met by the patient and in any case before the treatment start, all patients with an uncontrolled HCT (i.e. HCT ≥ 45%) have to perform phlebotomy(ies) to normalize the HCT value (i.e. HCT <45%).
In case of patients phlebotomy-dependent, all efforts have to be made by Investigators to record all phlebotomies witch recruited patients experienced at least 6 months before the treatment start.

4.5.4.2.4 Day 28 of Cycles 3 and 6

The following procedures will be performed at Day 28 of Cycles 3 and 6 of Part B (within ± 3 days) as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (if applicable);
- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status;
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN (see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin;
- ECG, QTc determination (according with Bazett's correction formula);
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- Spleen evaluation by MRI or CT scan;
- Collection of a blood sample for the quantitative RT-PCR evaluation of $JAK2^{V617F}$ mutational status on peripheral blood (PB) granulocyte;
- Assessment of disease-related symptoms using the MPN-SAF QOL Questionnaire **[24, 32]**;
- **Bone marrow histological evaluation (only for cycle 6), in patients who have consented to this optional exploratory research and that have not any medical contraindication to bone marrow sampling as judged by the Investigator;**
-

- Therapeutic response evaluation **according to the clinico-haematological ELN response criteria [21] (see paragraph 4.6.1);**
- **Therapeutic response evaluation according to the "new" ELN criteria (i.e. revised ELN response criteria) [33] (see paragraph 4.8.7) (only for cycle 6);**
- Givinostat administration and accountability **(only for cycle 3)**.

All phlebotomies performed in the first 3 weeks of treatment will be not counted to assess the ~~clinico-haematological~~**therapeutic** response.

4.5.4.2.5 End of study

The following procedures will be performed at the end of study visit (in case of completed study) or 7 days after last drug intake (in case of the patient drops-out of the study) (within ± 3 days) as reported below:

- Adverse event recording;
- Concomitant medications (drugs);
- Significant non-drug therapies (e.g. phlebotomies, transfusions) recording (if applicable);
- Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), weight, body temperature and ECOG performance status;
- Blood chemistry: ALT/SGPT, AST/SGOT, ALP, total bilirubin, LDH, creatinine, BUN (see Appendix F to convert Urea to BUN), glucose, Na, K, Ca, Cl, Mg, albumin;
- ECG, QTc determination (according with Bazett's correction formula);
- Haematology: RBC count, HCT, Hb, MCV, MCH, MCHC, WBC count (full and differential), PLT count;
- Spleen evaluation by MRI or CT scan;
- Collection of a blood sample for the quantitative RT-PCR evaluation of $JAK2^{V617F}$ mutational status on peripheral blood (PB) granulocyte;
- Assessment of disease-related symptoms using the MPN-SAF QOL Questionnaire **[24, 32]**;
- **Bone marrow histological evaluation, in patients who have consented to this optional exploratory research, and that have not any medical contraindication to bone marrow sampling as judged by the Investigator;**
- Therapeutic response evaluation **according to the clinico-haematological ELN response criteria [21] (see paragraph 4.6.1)**;
- **Therapeutic response evaluation according to the "new" ELN criteria (i.e. revised ELN response criteria) [33] (see paragraph 4.8.7);**
- Used/unused/partially used Givinostat supply return and accountability.

In case the patient drops-out the study during the first 3 Cycles (i.e. before the Day 28 of Cycle 3), this evaluation has not to be performed at End of Study visit.
At study close-out, and as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and the completed drug forms to Italfarmaco S.p.A. – Dipartimento di Tecnica Farmaceutica Viale Fulvio Testi, 330, 20126, Milan, Italy.
Only in some particular cases, after the authorization of Italfarmaco S.p.A. (or after a signed agreement between the investigational site and Italfarmaco S.p.A.), these materials can be destroyed locally.

4.6.1 Criteria for assessing clinico-haematological improvement
Disease response will be evaluated according to the following **clinico-haematological** ELN criteria [21] **(see paragraph 4.6.1)** 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 x10^9/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 will be evaluated according to the **clinico-haematological** ELN and EUMNET criteria [29] after 3 and 6 cycles of treatment with Givinostat, in ET and MF patients, respectively.

...

4.8.1 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 **[21] (see paragraph 4.6.1)** will be 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 will be used to evaluate the effect of Givinostat in ET and MF patients, respectively.

4.8.4 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) will be used, in order to assess the most important clinical symptoms among patients with MPNs [24~~, 32~~].
In addition, starting from MPN-SAF questionnaire, also the MPN-SAF Total Symptom Score [32] will be assessed as requested by the "new" ELN criteria (i.e. revised ELN response criteria) [32].

4.8.6 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 will be used. This assessment will be performed using the data entered by Investigators in the specific section of the CRF.

4.8.7 Evaluation of preliminary efficacy according to the revised ELN criteria

Disease response will be 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 [33] (see paragraph 4.8.7).

- **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 hemorrhagic 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 hemorrhagic 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) [33] (see paragraph 4.8.7):

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 [32].**

4.8.8 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) [33] (see paragraph 4.8.7) will be used to evaluate the effect of Givinostat in PV patients.

5.3 SAE Reporting

Any SAE, including death from any cause that occurs after a patient has signed the Informed Consent and up to the follow-up visit (regardless of relationship to study drug) must be reported by the Investigators to Italfarmaco S.p.A. within 24 hours of learning of its occurrence.

Related SAEs ***MUST*** be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed.

The Investigators are required to complete the SAE form provided by Italfarmaco S.p.A.. Sufficient details must be provided to allow for a complete medical assessment of the AE and independent determination of possible causality. The Investigators are obliged to pursue and provide additional information as requested by Italfarmaco S.p.A. Drug Safety Manager, or Study Director, or his designee.

The Investigator must notify the SAE to the Italfarmaco S.p.A. Drug Safety Unit (DSU) by faxing and/or mailing (only in case the mail will be automatically generated by the e-CRF) the SAE form, within 24 hours of a SAE, at the number specified below; then, only in case the SAE will be faxed to the Italfarmaco S.p.A. DSU, the Investigator must confirm any SAE notifications by mailing to the mail address or phoning to the phone number specified below:

PPD
Drug Safety Unit
Italfarmaco S.p.A.
Via dei Lavoratori, 54
20092 Cinisello Balsamo (MI), Italy
Phone: PPD
Mobile: PPD
Fax: PPD
e-mail: PPD

The same procedure must be applied to the SAE follow-up information.

All serious and unexpected AE that are associated with the use of the study drug (SUSARs) will be notified by Italfarmaco S.p.A. Drug Safety Manager to the competent authority within the required time and following procedures required by applicable laws.

It is imperative that Italfarmaco S.p.A. be informed as soon as possible, so that reporting can be done within the required time frame.

The SAEs will also be recorded in the dedicated AE section of the CRF.

5.3.2 Pregnacy

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 shall be immediately stopped. The investigator is required to report the pregnancy to Italfarmaco S.p.A. Drug Safety Unit (DSU) within 24 hours via telephone and/or fax and/or mail (only in case the mail will be automatically generated by the e-CRF). If initially reported via telephone, this must be followed-up with a written report via fax and/or mail (only in case the mail will be automatically generated by the e-CRF) within 24 hours of the telephone report.
Patients should be instructed to notify the investigator if, after completion of the study, it is determined that they became pregnant during the treatment phase or ~~within the last follow up visit~~ **through 3 months after the last dose of study drug**.
Whenever possible, a pregnancy with an onset within the above defined time frame should be followed until termination, any premature termination should be reported, and the status of the mother and child should be reported to the sponsor after delivery.
If the Investigator is made aware that the partner of a male patient who is participating to the study become pregnant, he/she is required to report the pregnancy to Italfarmaco S.p.A. DSU within 24 hours via telephone and/or fax and/or mail (only in case the mail will be automatically generated by the e-CRF). If initially reported via telephone, this must be followed-up with a written report via fax and/or mail (only in case the mail will be automatically generated by the e-CRF) within 24 hours of the telephone report.
Whenever possible, such pregnancy should be followed until termination, any premature termination should be reported, and the status of the mother and child should be reported to the sponsor after delivery.

6.2.6.1 Part A

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

- Preliminary efficacy of Givinostat (secondary endpoint) for PV/ET and MF patients, respectively (see paragraph 4.6.1 for more details):
  - For PV and ET (if any): Complete response (CR) and partial response (PR) rate according to the clinico-haematological ELN response criteria **[21]** (see paragraph 4.6.1);
  - For MF (if any): Complete response (CR), major response, moderate response and minor response rate according to the EUMNET response criteria (see paragraph 4.6.1).

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 may be expanded to all patients with cMPN.

Frequency and percentage of patients in each response category (complete response (CR), partial response (PR), no response (NR) for PV and ET; Complete response (CR), major response, moderate response and minor response rate for MF) will be presented at each time point. In order to evaluate the response rate, subjects who discontinued prematurely the study for any reason (AE, consent withdrawal, lost to follow up) will be defined as 'Non Responder'. 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 dose cohort along with descriptive statistics.

The PK analysis will be conducted on the PK population.

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. These tables will include number of observations, mean, standard deviation, median, minimum and maximum and additionally the geometric mean and coefficient of variation (not for time to maximum plasma concentration).

6.2.6.2 Part B

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

- Preliminary effectiveness of Givinostat (secondary endpoint) after 6 cycles of treatment in Part B for PV/ET and MF patients, respectively (see paragraph 4.6.1 for more details):
  - For PV and ET (if any): Complete response (CR) and partial response (PR) rate according to the clinico-haematological ELN response criteria **[21]** (see paragraph 4.6.1);
  - For MF (if any): Complete response (CR), major response, moderate response and minor response rate according to the EUMNET response criteria (see paragraph 4.6.1).

  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 may be expanded to all patients with cMPN.

  Frequency and percentage of patients in each response category (complete response (CR), partial response (PR), no response (NR) for PV and ET; Complete response (CR), major response, moderate response and minor response rate for MF) will be presented at each time point. In order to evaluate the response rate, subjects who discontinued prematurely the study for any reason (AE, consent withdrawal, lost to follow up) will be defined as 'Non Responder'. 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 the end of Cycles 6, or including data related to Cycles 4, 5 and 6) based on safety population:

- 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 most updated version). Adverse events (AEs) will be reported on a per subject basis. If a patient has more than one AE for a treatment that coded to the same preferred term (PT), the patient will be counted only once for that preferred term. Similarly, if a patient has more than one AE for a treatment within a system organ class (SOC) category, the patient will be counted only once in that system organ class category. A patient with multiple CTCAE grades for an AE will be summarized under the maximum CTCAE grade recorded for the event.

Any Adverse Events which started at or after the first administration of study treatment 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 treatment emergent.

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 subjects with at least one AE, at least one TEAE, at least one drug-related TEAE, at least one serious TEAE, 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 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 (not for time to maximum plasma concentration).

6.2.7.1 Parts A and B

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

- The effect of Givinostat on each single response parameter according to the **clinico-haematological** ELN (for PV and ET) **[21] (see paragraph 4.6.1)** and EUMNET response criteria (for MF); 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 may 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 [24, **32**~~θ~~].
- Reduction of the $JAK2^{V617F}$ 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 and PP:

- **The preliminary efficacy of Givinostat after 6 cycles of treatment according to the "new" ELN criteria (i.e. revised ELN response criteria) [33] (see paragraph 4.8.7).**
- **The effect of Givinostat on single parameters of the "new" ELN criteria (i.e. revised ELN response criteria) [33] (see paragraph 4.8.7).**

Explorative endpoints will be summarized by descriptive methods. Default summary statistics and changes from baseline (where applicable) to each time point for all parameters will be produced.

6.3 Sample size and power considerations

The A standard 3+3 design adopting a modified Fibonacci escalation schema will be used in Part A [25, 26, 27].

Sample size for Part B was discussed for the primary end point defined as the Overall Response Rate after 3 cycles. Simon's 2-stage design will be employed in Part B [30] with the aim of testing the "null hypothesis" that RR ≤ 0.50 versus the "alternative" that RR ≥ 0.75. Response rate will be assessed as defined in paragraph 6.2.5.2. Overall up to 28 patients will need to be recruited, 12 patients being enrolled in Stage-1. PV patients enrolled at the ~~RP2D~~**MTD** in Part A may be counted towards Stage 1. Under the "null hypothesis" (if RR = 0.50), the expected total sample size is of 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 favour 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 respond to the treatment the trial will be terminated rejecting the "alternative" that RR ≥ 0.75. Otherwise, the trial goes on to Stage-2 enrolling further 16 patients to a total of 28 patients. If at the end of Stage-2, a total of 17 or fewer patients respond to the treatment the "alternative hypothesis" that RR ≥ 0.75 will be rejected; alternatively, if 18 or more patients respond, the "null hypothesis" that RR ≤ 0.50 will be rejected. Estimations are obtained from proprietary software (based on SAS ® 9.2) according to the algorithm proposed by R. Simon [30].

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