NOVARTIS

Clinical Development

Panobinostat

CLBH589H2101 / NCT00946647

A phase Ib/IIb, open-label, multi-center, dose-escalation study of oral Panobinostat (LBH589) administered with 5-Azacitidine (Vidaza®) in adult patients with Myelodysplastic Syndromes (MDS), Chronic Myelomonocytic Leukemia (CMML) or Acute Myeloid Leukemia (AML)

RAP Module 3 – Detailed Statistical Methodology (Amendment 2)

Author: [redacted]

Document type: RAP Documentation

Document status: Version 2.1, Final

Release date: 29-Oct-2014

Change history

CREDI Version	Date	Changes
Amendment 1	23-Jun-2014	Analysis plans corresponding to the phase IIb part have been added Minor changes to existing analysis descriptions have been made to align with the current project MAP [redacted]
Amendment 2	29-Oct-2014	The sections on dose intensity calculation in the M3 were revised to simplify definitions of dose intensity and relative dose intensity, as they applied to this study. For the purpose of dose intensity calculations, a general algorithm was put in place to assign doses to days.

Table of contents

Abbreviations

Abbreviation	Detail
5-Aza	5-Azacytidine, trade name: Vidaza®
AE	Adverse event
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
ATC	Anatomical, therapeutical, chemical
BLRM	Bayesian logistic regression model
bpm	beats per minute
BSA	body surface area
CMML	Chronic myelomonocytic leukemia
CNAE	Clinical notable adverse event
CNS	central nervous system
CR	Complete remission
CRF	Case report form

Abbreviation	Detail
CRi	Complete remission with incomplete blood count recovery
CSR	Clinical study report
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DAR	Dose administration record
DLT	Dose-limiting toxicity
ECG	12 lead electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EWOC	Escalation with overdose control
FAB	French-American-British
FAS	Full analysis set
HI	Hematologic improvement
HSCT	Hematopoeitic stem cell transplantation
IPSS	International prognostic scoring system
LLOQ	Lower limit of quantitation
MAP	Master analysis plan
MDS	myelodysplastic syndrome
MedDRA	medical dictionary for regulatory activities
ms	Milliseconds
MTD	Maximum tolerated dose
NCI	National cancer institute
PAN	Panobinostat
PK	Pharmacokinetic
PR	Partial remission
PT	Preferred Term (category of MedDRA)
RAP	Report and analysis plan
SAE	Serious Adverse Event
SD	Stable disease
SI	Système internationale
SOC	System organ class (category of MedDRA)
T4	thyroxine
TSH	thyroid stimulating hormone
VAP	Validation and planning
WHO	World Health Organization

1 Introduction

Document content

This RAP module describes the planned statistical methods. It is structured as

- A draft of Section 9.7 of the clinical study report (CSR) [Statistical methods planned in the protocol and determination of sample size]
- A draft of Appendix 16.1.9 (Documentation of statistical methods).

Appendix 16.1.9 text will contain details of statistical methods and issues that are too long to include in the CSR text. (Appendix 16.1.9 is not mandatory for abbreviated and synoptic reports).

It is written in future tense. It will be reviewed and updated (including conversion to past tense) for entry into the CSR after the statistical analysis has taken place.

The data will be analyzed by Novartis and/or designated CRO. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

It is planned that the data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for **analysis**. Data from the phase Ib and phase IIb parts will be separately analyzed, but presented in the same CSR. Unless, otherwise specified in this document, the same conventions and working definitions will apply to analyses conducted in the two phases of this study.

The core CSR, encompassing both phase Ib and phase IIb parts, will be based on a data cut-off corresponding to the time point where all patients from the phase IIb part have either completed 12 cycles of study treatment or discontinued study treatment for any reason whichever comes first. An addendum to the core clinical study report will be provided at the time of completion of the study to summarize and/or list the additional safety and efficacy data as appropriate. Patients who are continuing their treatment at the time of data cut-off and are assessed by the Investigator to have the potential to benefit from their treatment will continue their assigned treatment on a reduced assessment schedule allowing collection and review of safety, efficacy, and survival data.

2 Study design

This is an open-label, multi-center, phase Ib/IIb study. The phase Ib part of the study is designed to determine the maximum tolerated dose (MTD) and/or the recommended phase II dose (RPIID) of panobinostat administered in a fixed combination of 5-Aza in adult patients with IPSS INT-2 or high-risk MDS, CMML or AML not eligible for HSCT.

The phase IIb part, that will commence once MTD and/or RPIID is established, has a randomized, two arm design and is designed to assess preliminary efficacy of panobinostat (in combination with 5-Aza) at RPIID compared to 5-Aza alone, the current standard of care, and to further characterize safety and tolerability of this combination.

In the phase Ib part, patients will receive escalating oral doses of the study drug panobinostat. The starting dose of Panobinostat will be 10 mg and will be administered intermittently (Day 3, 5, 8, 10, 12, and 15) over 2 weeks. As per registered label, 5-Aza will be given subcutaneously (sc) at a dose of 75 mg/m^2/day for 1 week (Day 1- 7). A treatment cycle is defined as 28 Days in duration. Patients should be treated for a minimum of 6 cycles. Study treatment should be continued as long as the patient continues to benefit or until disease

progression or unacceptable toxicity is encountered or consent withdrawal whatever comes first.

At least 3 patients per cohort must be enrolled. During the phase Ib part, patients will be evaluated for DLT (Section 6.6.1.6 of the protocol) using an adaptive Bayesian logistic regression model with overdose control (EWOC) to guide the dose escalation process.

After completion of a given dose cohort, the decision on the dose chosen for the next cohort will depend on the risk assessment using the Bayesian logistic regression method and a medical review of available clinical and laboratory data. Dose-limiting toxicity will be assessed from the safety data of Cycle 1 for each dose level. Prior to declaring a dose to be MTD, at least 9 evaluable patients need to be treated at that dose level.

The MTD is defined to be the highest daily dose of panobinostat given together with 5-Aza in the first treatment cycle in which the probability to produce medically unacceptable, dose limiting toxicity (DLT) in more than 35% of the patients is less or equal to 25%. The recommended phase II dose (RPIID) will be based on considerations of the MTD estimation process by the adaptive Bayesian logistic regression model, and on an overall assessment of safety taking into consideration tolerability data from subsequent cycles at all the different dose levels tested.

As of August 2011, the recommended phase II dose (RPIID) has been determined to be 30 mg of oral panobinostat once daily on day 3, 5, 8, 10, 12, and 15 in combination with azacytidine (5-Aza/Vidaza®) administered at a dose of 75mg/m^2 daily for 7 days).

Additional 80 patients will be randomly assigned in a 1:1 ratio into the phase IIb part of the study receiving 30 mg of panobinostat plus 5-Aza (investigational arm) or single agent 5-Aza (active control arm). Single agent 5-Aza will be administered according to the locally approved label (75mg/m^2 daily for 7 days).

Patients will continue treatment until disease progression, unacceptable toxicity or consent withdrawal, whichever comes first. The core clinical study report (encompassing both, the phase Ib and the phase IIb part of the study) will be based on a data cut-off corresponding to the time point where all patients have either completed 12 cycles of study treatment in phase IIb or discontinued study treatment for any reason whichever comes first. An addendum to the core clinical study report will be provided at the completion of the study to summarize and/or list the additional safety and efficacy data as appropriate.

Patients who are continuing their treatment at the time of data cut-off for the core CSR and are assessed by the Investigator to have the potential to benefit from ongoing treatment will continue their assigned treatment allowing collecting and reviewing safety, efficacy and survival data. After the data-cut off point for the core CSR, a reduced visit evaluation schedule will be applied.

3 Objectives

3.1 Phase Ib part

3.1.1 Primary objective

- To determine the MTD and/or RPIID of oral panobinostat in combination with a fixed dose of 5-Aza in adult patients with IPSS INT-2 or high risk MDS, CMML, or AML.

3.1.1.1 End-point for primary objective

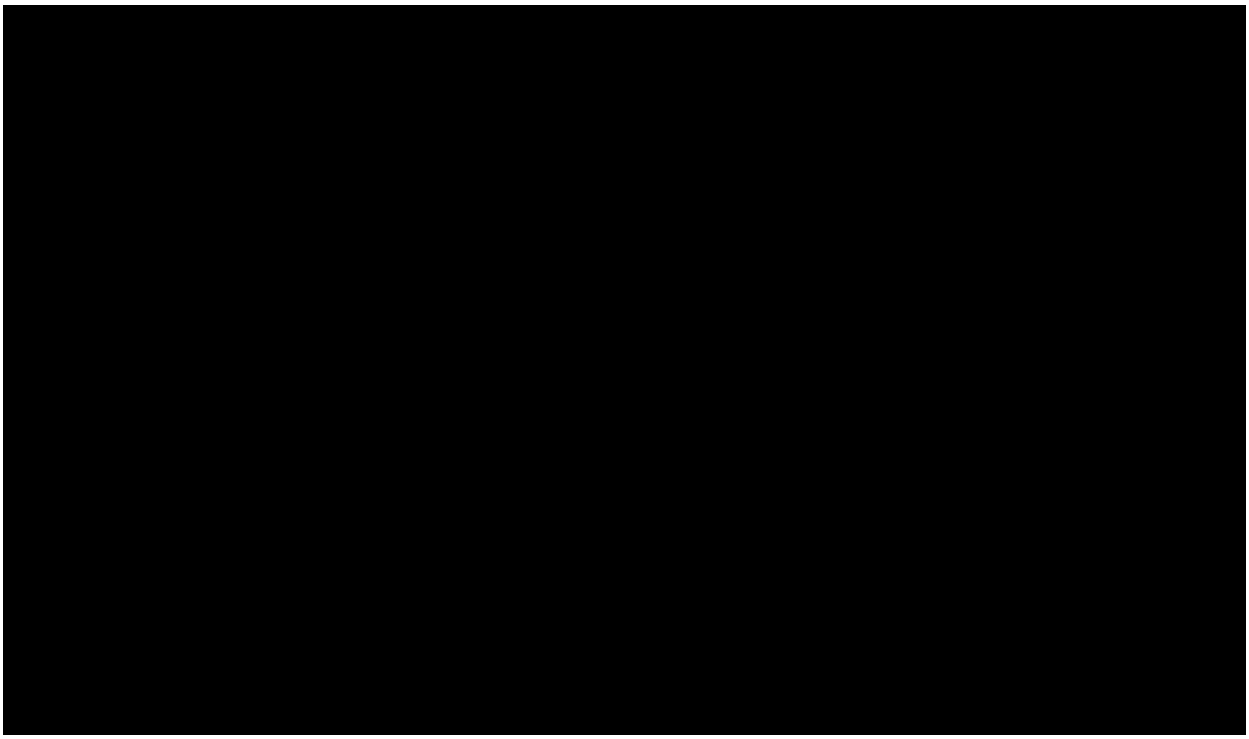
- Incidence of DLT

3.1.2 Secondary objectives

- To characterize the safety and tolerability of panobinostat in combination with 5-Aza in the target patient population.

3.1.2.1 End-points for secondary objectives

- Type, duration, frequency and relatedness of Adverse Events (AE). AE severity will also be assessed according to NCI Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
- Laboratory (biochemistry, hematology)
- ECG monitoring (central review by eRT)



3.2 Phase IIb part

3.2.1 Primary objective

- To assess preliminary efficacy of treatment with the panobinostat and 5-Aza combination at the RPIID relative to treatment with single agent 5-Aza through the assessment of composite CR (CR or CRi or bone marrow CR).

3.2.1.1 End-point for primary objective

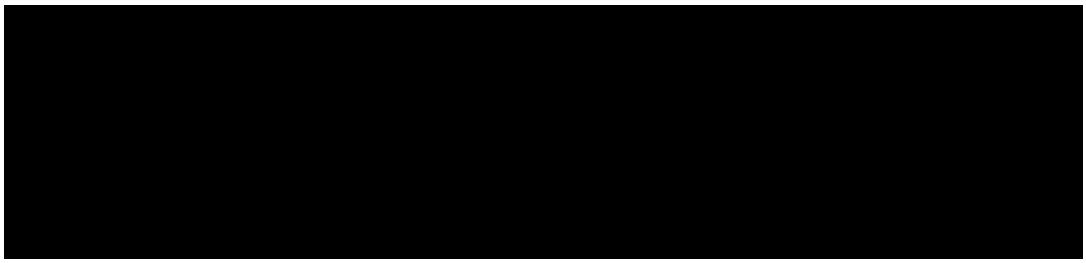
- Composite CR (CR or CRi or bone marrow CR)

3.2.2 Secondary objectives

- To assess preliminary efficacy of treatment with the panobinostat and 5-Aza combination at the RPIID relative to treatment with single agent 5-Aza through the assessment of clinical responses other than the composite CR specified in the primary objective, 1 year survival, and time to progression (TTP).
- To characterize the safety and tolerability of panobinostat at the RPIID in combination with 5-Aza, as well as, 5-Aza alone in the target patient population.

3.2.2.1 End-points for secondary objectives

- Clinical response for AML: PR; for MDS/CMML: PR, Hematologic Improvement (HI)
- Overall response (CR or CRi or bone marrow CR or PR)
- 1-year survival rate
- Time to progression (TTP) based on the Guidelines for Implementation of IWG response criteria in AML, MDS and CMML according to Cheson 2003 and 2006 and specified in [Post-text supplement 1].
- Type, duration, frequency and relatedness of Adverse Events (AE). AE severity will be assessed according to NCI Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
- Laboratory (biochemistry, hematology)
- ECG monitoring (central review by eRT)



4 Population

Adult patients with intermediate-2 or high-risk MDS as per IPSS, AML with multilineage dysplasia and maximum of 30% bone marrow blasts (former RAEB-T according to FAB, currently AML according to WHO definition),), or Chronic Myelomonocytic Leukemia (CMML) who are candidates for the treatment with 5-Aza will be enrolled onto the study.

5 Draft of Section 9.7 of CSR on Statistical methods

5.1 Statistical methods and data analysis

5.1.1 Phase Ib part

An adaptive Bayesian logistic regression model (BLRM) and dose-escalation criteria similar to that proposed by (Babb, Rogatko and Zacks 1998) including the escalation with overdose control (EWOC) principle will be used to guide the dose escalation to determine the MTD of PAN in combination with a fixed dose of 5-Aza. Informative priors for PAN will be derived based on the DLT rate obtained from a similar trial [CLBH589B2102, arm X] with similar populations, formulations, dose regimens and for 5-Aza from publications. The MTD will be assessed during the first treatment cycle. Each cohort will consist of a minimum of 3 patients fully evaluable for therapy-related toxicities over the first cycle of treatment. Posterior probabilities of the DLT from the model will be summarized. Selection of the next dose will be based on these probabilities as well as on other safety and laboratory data. For details please refer to the Post-text supplement 2.

Dose recommendation will be based on posterior summaries for each dose combination and the interval probabilities for underdosing, targeted, excessive, and unacceptable toxicity for intervals. Once updated, the distribution summarizes the probability that the true probability of a DLT for each dose combination lies in 1 of the following categories:

- [0, 20%) under-dosing
- [20%, 35%) targeted toxicity
- [35%,60%) excessive toxicity
- [60, 100%] unacceptable toxicity.

Following the principle of EWOC, the recommended dose combination is the one with the highest posterior probability of DLT in the target interval [20%, 35%) among the doses fulfilling the overdose criteria after each cohort of patients: there is less than 25% chance of either excessive or unacceptable toxicity. The maximum inter-cohort dose escalation permitted is 100%. The dose recommended by the adaptive BLRM may be regarded as information to be integrated with a clinical assessment of the safety data observed thus far in determining the next dose to be investigated. In any case, the next dose will not exceed the recommended dose by the BLRM. Cohorts of at least 3 and up to a maximum of 12 MTD evaluable patients will be enrolled in the dose-escalation part including at least 9 patients at the MTD. The Bayesian model will be updated prior to additional enrollment under the following scenarios:

1. If the first 2 patients in a cohort experience DLT prior to the enrollment of the 3rd patient enrollment will be halted, the model will be updated, and any new patients will be enrolled at a dose satisfying the overdose criteria, no higher than the current dose level.
2. No additional patients will be enrolled until the current cohort is completed and the model is updated.
3. For cohorts of > 3 patients if the observed number of DLTs exceeds 25% of the currently enrolled patients to that dose level, enrollment will be halted until all patients complete 1 cycle of dosing or experience DLT. The model will be updated to determine the

uncertainty about the probability of DLT at each dose level. New patients will be enrolled at a dose level up to the highest satisfying the overdose criteria.

Estimation of the MTD will be based upon the estimation of the probability of DLT in cycle 1 in the MTD determining set. Estimation of the RPIID will be based on considerations of the MTD estimation process by the use of the BLRM, together with an overall clinical assessment of safety taking into consideration safety and tolerability data from all cycles. The RPIID could be the same as the MTD, but will not exceed it under any circumstance. Cohorts may be expanded at any dose level (or dose combination) below the MTD for further elaboration of safety parameters as required.

For further details of the statistical model and results under a variety of scenarios, please refer to Clinical Study Protocol Post-text supplement 2.

5.1.2 Phase IIb part

There will be no formal testing of statistical hypotheses. Descriptive summaries of safety and efficacy by treatment group will be provided. Point estimates of efficacy endpoints (such as response rate) along with appropriate confidence intervals may be reported by treatment group.

5.2 Populations for analysis: definitions

5.2.1 Phase Ib part

Safety Set: The safety set includes all patients who received at least 1 dose of any 1 compound of the study treatment.

MTD-determining set: consists of all patients of the safety set who either received sufficient study treatment as defined in the minimum exposure criteria in cycle 1 (patients need to have 100% of the planned dose of each compound, see Table 5-1) and had sufficient safety evaluations or discontinued due to DLT in Cycle 1. Patients who do not meet these minimum safety evaluation requirements in cycle 1 will be regarded as ineligible for the MTD-determining set. From a programming point, a patient will be considered to have sufficient safety evaluations if he or she has information on vital signs and/or lab assessments taken during cycle 1. The information on whether a patient experienced a DLT during cycle 1 will be taken from the 'End-Of-Cycle' page for the first cycle.

Table 5-1 Minimum exposure criteria (Cycle 1)

Compound	Scheduled doses	Minimum exposure criterion
PAN	6	6
5-Aza	7	7

Full analysis set: This will be the same as the safety set.

PK set: consisted of all patients with at least 1 evaluable PK profile of PAN.

5.2.2 Phase IIb part

Safety Set: The safety set includes all patients who received at least one dose of any one component of the study treatment. Patients in the safety set will be analyzed as treated. The

"as treated" information will be taken from the IVRS medication package that was actually dispensed. However, patients who are randomized to the PAN+5-Aza group, and have not taken a non-zero dose of PAN as per the DAR panel, at the time of data cutoff, will be reported under the 5-Aza group for analyses based on the safety set.

Full analysis set: consists of all patients who were randomized to one of the two treatment arms. Following the intent-to-treat (ITT) principle, the patients in the FAS will be analyzed in the treatment group they were assigned to at randomization. The randomized treatment information will be taken from the IVRS patient randomization listing.

5.3 Population and grouping for the analyses

For all safety analyses in phase Ib/IIb, the safety set will be used. The FAS will be used for all efficacy analyses, as well as, for analysis of patient disposition, demography and baseline characteristics in phase Ib/IIb. For the determination of the MTD in phase Ib part, the MTD-determining set will be used. For the analysis of PK data in phase Ib part, the PK set will be used. The MTD determining set and the PK set are defined and applicable only for the phase Ib part.

5.4 Patient disposition, demographics and other baseline characteristics

Patient disposition, demographic and other baseline data will be listed by patient and/or summarized descriptively by initial dose group of PAN in the phase Ib part, and, by treatment group in the phase IIb part. The analyses will be based on the full analysis set. Categorical data will be presented as frequencies and percentages. For continuous data, summary statistics will be presented including mean, standard deviation, median, minimum, and maximum.

5.5 Treatments (study drug, concomitant therapies, compliance)

The actual dose and duration in days of PAN and 5-Aza as well as the actual dose intensity (computed as cumulative dose received / actual duration) and relative dose intensity (computed as actual dose intensity / planned dose intensity [= planned cumulative dose / scheduled duration]), will be listed and summarized by means of descriptive statistics by initial dose group of PAN in the phase Ib part, and, by treatment group in the phase IIb part.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized by ATC term descriptively.

5.6 Pharmacokinetics

Trough plasma PAN sample levels collected during Cycle 1 of the phase Ib part of the study, on Days 4, 5, and 8 will be summarized by study day. Concentrations of pre-dose levels of PAN (Cmin values) will be summarized at the study conclusion by study day and actual dose group of PAN. Values below the lower limit of quantification (LLOQ) of approximately 0.5 ng/mL will be reported as 0 ng/mL. Missing values will be labeled accordingly.

5.7 Safety variables and analyses

5.7.1 Adverse events (AE)

All AEs recorded during the study will be summarized. The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by system organ class, severity (based on the National Cancer Institute's Common Terminology Criteria for Adverse Events [NCI CTCAE version 3]), type of AE and relation to the study treatment. SAEs resulting in death and non-fatal serious AEs (SAEs) will be listed by patient and tabulated by type of AE and initial dose group of PAN.

Listings of deaths, SAEs, AEs requiring dose interruption or adjustment, AEs requiring additional therapy, Grade 3/4 AEs, and AEs leading to early termination of study treatment or premature withdrawal from study will be also provided.

5.7.2 Laboratory abnormalities

All laboratory values for hematology, biochemistry, coagulation, free T4, TSH and urinalysis will be converted into SI units, if appropriate, and the severity Grade calculated using appropriate common toxicity criteria (CTC).

By-patient listings of laboratory values will be provided by laboratory parameter and patient. Separate listings will display notable laboratory abnormalities based on the laboratory normal ranges. The frequency of laboratory abnormalities will be displayed by parameter. Laboratory data will be summarized by presenting shift tables by initial dose group of PAN.

5.7.3 Other safety data

Data from ECGs, vital signs and ECOG performance status will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. Any QT and QTcF outliers (as defined in section 4.10.6 on ECG in the later part of this document) will be summarized and listed.

5.7.4 Tolerability

Not applicable.

5.8 Efficacy variables and analyses

5.8.1 Phase Ib part

Summaries of the following efficacy endpoints will be reported by initial dose group of PAN.

- Clinical response for AML: complete remission (CR), complete remission with incomplete blood count recovery (CRi), partial remission (PR)
- Clinical response for MDS/CMML: CR, bone marrow CR, PR, hematologic improvement (HI)

Evidence of anti-leukemic activity of PAN in combination with 5-Aza will be evaluated using best response based on the Novartis' implementation of the recommendations of the 'International Working Group for Diagnosis, Standardization of response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in MDS and Acute Myeloid Leukemia' (Cheson 2003, Cheson 2006) as implemented in Post-text supplement 1. The best on-study response as categorized by the response criteria will be listed by patient, as well as, summarized, based on investigator's assessment. Exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated Clopper and Pearson 1934.

5.8.2 Phase IIb part

The primary efficacy endpoint will be the composite CR (CR or CRi or bone marrow CR) among all patients in the FAS.

The following efficacy endpoints will be considered.

- Clinical response for AML: CR, CRi, PR
- Clinical response for MDS/CMML: CR, bone marrow CR, PR and Hematologic Improvement (HI)
- 1-year survival rate
- Time to Progression (TTP)

Clinical responses will be summarized by treatment arm, overall and within disease type (i.e. AML or MDS/CMML). Percentage rates for the composite CR rate (CR or CRi or bone marrow CR), overall response rate (CR or CRi or bone marrow CR or PR) will be reported along with 95% confidence intervals for both arms. Exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated (Clopper and Pearson 1934.). Point estimates and confidence intervals for the difference in rates between the treatment arms will also be reported. The 1-year survival rate will be obtained from the Kaplan-Meier curve and its variance will be estimated by Greenwood's formula. Time to progression will also be analyzed through Kaplan Meier curves.

5.10 Handling of missing values/censoring/discontinuations

Patients who are not evaluable for MTD determination (i.e. patients who are not in MTD determining set) will be replaced. Patients in whom clinical response is unknown will be treated as non-responders. Patients, for whom the post-baseline response assessments cannot be computed because of missing baseline response assessment, will be deemed as patients with 'unknown' response. Other missing data will be noted as missing on appropriate tables/listings.

5.11 Subgroup analyses

No subgroup analyses will be performed.

5.12 Interim analysis

Not applicable.

5.13 Sample size calculation

5.13.1 Phase Ib part

Sample size is expected to be 26 in total. Cohorts of at least three MTD evaluable patients per dose level will be enrolled in the phase Ib part including at least nine patients at the MTD and/or RPIID level.

Sample size is expected to be at least 26 assuming two cohorts of six patients each treated at dose levels distinct from the MTD and/or RPIID, and two cohorts of 7 patients each treated at the MTD and/or RPIID.

5.13.2 Phase IIb part

The planned sample size is 40 per arm, or, in other words, 80 in total. It is deemed that an observed relative improvement of 50% in the composite CR rate (CR or CRi or bone marrow CR) in the investigational arm over the active control arm is clinically relevant in the phase IIb part of the study. Under the assumption that the composite response rate in the active control arm is 17% (estimate based on Fenaux et al 2009a), the following table gives the estimated probabilities of observing clinically relevant improvement , under different values of the true composite CR rate in the experimental arm. The chance of observing a clinically relevant improvement when there is actually no difference in the true composite CR rates between the arms) is estimated to be 23% while the chance of not observing a clinically relevant improvement when there is indeed a substantial difference in the true composite CR rates (true composite response rates in investigational and active control arms are 35% and 17% respectively) is estimated to be 19%. Since there is no hypothesis being tested, a formal power analysis has not been done. The aforementioned estimated probabilities of 23% and 19% are only analogous to the probabilities of type I and type II errors (in the setting of hypothesis testing). These probabilities (as well as, the others shown under [4] in the following table) have been derived by simulating response data using independent binomial distributions for the investigational and active control arms with the probability parameter of the distribution being specified according to the assumed true underlying composite CR rates as shown under [1], and [2] of the table below. Thus, given that the true composite CR rates are as in [1] and [2] (and, the true percentage improvement as in [3]), [4] represents the probability of observing clinically relevant improvement. More specifically, [4] represents the following:

Pr[(observed composite CR rate in investigational arm - observed composite CR rate in active control arm) ≥ 50% of observed composite CR rate in active control arm]

Table 5-2 Probability of observing clinically relevant improvement based on an assessment of composite CR (CR or CRi or bone marrow CR)

True composite CR rate in active control arm	True composite CR rate in investigational arm	True improvement (as a percentage of the true composite CR rate	Probability of observing clinically relevant improvement

[1]	[2]	in the active control arm) [3]	[4]
0.17	0.17	0	0.23
	0.20	18	0.33
	0.25	47	0.51
	0.30	76	0.68
	0.35	106	0.81

5.14 Power for analysis of critical secondary variables

There is no critical secondary variable.

[redacted]

Draft of Appendix 16.1.9

Clinical Development

Panobinostat

Appendix 16.1.9: Documentation of statistical methods

Document type: Clinical Study Report - Appendix 16.1.9

1 Table of contents

2 Introduction

The statistical methodology used (Section 9.7) will be described and discussed in the main part of the clinical study report. In Appendix 16.1.9, details of the statistical methods and their justification are provided for the statistical reviewers.

The statistical analysis of this study will be performed by Novartis personnel. SAS® version 9.2 (SAS Institute Inc., Cary, NC, USA) will be used for all analyses. The simulations for the adaptive Bayesian logistic regression model (BLRM) will be performed by WinBUGS for Windows® version 1.4 and R for Windows® version 2.8 using the module OncoBayes developed internally by Novartis. All data are part of the Clinical Database and will be exported to SAS® files for analysis.

3 Definitions and general methodology

3.1 Definitions

3.1.1 Study drug and study treatment

3.1.2 Phase Ib part

Study drug refers to single agent PAN.

Study treatment refers to of PAN plus 5-Aza (combination therapy).

Study combination partner refers to 5-Aza.

3.1.3 Phase IIb part

Study drug refers to single agent PAN in the treatment arm and to 5-Aza in the control arm.

Study treatment refers to of PAN plus 5-Aza (combination therapy) in the treatment arm and to 5-Aza alone in the control arm.

Study combination partner refers to 5-Aza in the treatment arm. There is no *study combination* partner in the control arm.

3.1.4 Date of first administration of study drug

The date of first administration of study drug is derived as the first date when a nonzero dose of study drug was administered and recorded on the dose administration record (DAR) case report form (CRF). For the sake of simplicity, the date of first administration of study drug will also be referred as *start of study drug*.

3.1.5 Date of last administration of study drug

The date of last administration of study drug is defined as the last date when a non-zero dose of study drug was administered and recorded on the *end-of-treatment* CRF.

3.1.6 Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a non-zero dose of any component of study treatment was administered and recorded on DAR CRF. For example, if in the phase Ib part, the 1st dose of PAN is administered on 05JAN2010, and the 1st dose of 5-Aza is administered on 03JAN2010, the date of first administration of study treatment is on 03JAN2010. For the sake of simplicity, the date of first administration of study treatment will also be referred as the *start of study treatment*.

3.1.7 Date of last administration of study treatment

The date of last administration of study treatment is derived as the last date when a non-zero dose of any component of study treatment was administered and recorded on end-of-treatment CRF. For example, if in the phase Ib part, the last dose of PAN dose is administered on

15APR2010, the last dose of 5-Aza is administered on 17MAY2010, the date of last administration of study treatment is then on 17MAY2010.

3.1.8 Study day

3.1.8.1 Phase Ib part

The study day *for all assessments* (efficacy, safety) will be calculated as the difference between the date of the event (e.g., visit date, onset date of an event, assessment date) and the treatment start date plus 1 day. The first day of study treatment is therefore Study Day 1. For example: if the start of study treatment is on 05JAN2010 and the start date of an Adverse Event (AE) is on 09JAN2010, the study day of the AE onset is calculated to have occurred on Study Day 5.

If the event or assessment date happens to be before the treatment start date, the calculation will be without "+1" and the resulting day(s) is a negative number.

3.1.8.2 Phase IIb part

The study day *for safety assessments* (e.g., adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption etc.) will be calculated as:

Date of the assessment/event - start date of study treatment + 1.

The study day *for all other, i.e. non-safety assessments/events* (e.g., response assessment, disease progression, ECOG performance status, etc.) will be calculated as:

Date of assessment/event - randomization date + 1.

Example: if randomization date is 02-Jan-2011, start of study treatment is on 05JAN2011, and the date of death is 09JAN2011 then the study day when the death occurred is 8.

For events that occur before randomization/first treatment day, the "+1" from the

formulas above will be removed and the study day will be a negative number by definition:

Study day = Event date - Date of first study treatment/randomization.

Note that the day of first dose of study treatment is day 1 and the day before the date of first study treatment is day – 1, not day 0.

Death may be analyzed as a safety or an efficacy variable depending on the context.

If death is analyzed as a safety variable (such as a listing of deaths), then "study day" must be calculated following the rules for safety assessment. When death is used as an efficacy variable , such as, in the analysis of overall survival or progression-free-survival, then the non-safety rule must be used.

3.1.9 Baseline

Baseline is the result of an investigation describing the "true" uninfluenced state of the patient.

Phase Ib part (non-randomized):

Baseline is defined to be the last available value or assessment, assessed prior to or on the date of start of study treatment.

Phase IIb part (randomized):

For ***efficacy evaluations***, the last available assessment before or on the date of randomization is taken as "baseline" value or assessment. In the context of baseline definition, the efficacy evaluations include ECOG performance status.

For ***safety evaluations*** (i.e. AEs, laboratory values, and vital signs), the last available assessment before or on the date of start of study treatment, is taken as "baseline' assessment. For ECG, please refer to section 3.8.5.

If patients have no value as defined above, the baseline result will be considered to be missing. Any assessment which is obtained outside of the protocol-defined screening period will not be considered for baseline unless otherwise specified.

Baseline definition for ECG assessments is given in section 4.9.6.

3.1.10 On-treatment assessment/event/period

On-treatment assessment/event is any assessment/event obtained in the on-treatment period which is defined as the following time interval:

> [date of first administration of study treatment; date of last administration of study treatment +28 days], i.e. inclusive of the lower and upper limits.

The calculation of study treatment duration may use different rules as specified in Section 3.5.1.

3.1.11 Time windows

For response assessment, the time window as defined in Clinical Study Protocol Post-text supplement 1 to the protocol will be applied.

3.1.12 Screening failure

Screening failures are patients who will have been enrolled but subsequently fail the screening criteria on the study. These patients will not be treated.

3.2 Data included in analyses

A unique data cut-off date will be determined. Only data from an assessment or event start date (e.g., vital sign assessment date or start date of an AE) prior to or on the cut-off date will be included in the analysis. For example, if the cut-off date is 15JUN2011, an AE starting on 13JUN2011 will be reported, whereas an AE with a start date of 17JUN2011 will not be reported.

All events with a start date before or on the cut-off date and an end date after the cut-off date will be reported as 'continuing at the cut-off date'. The same rule will be applied to events

starting before or on the cut-off date and not having a documented end date. This approach applies in particular to AE and concomitant medication reports.

If imputation of an end date is required for a specific analysis (e.g., for a dose administration record with a missing end date or an end date after the cut-off date, the latter of which must be imputed as an end date to allow for the calculation of treatment exposure duration), the imputed date will be displayed and flagged in the listings.

The data cut-off date for the core CSR will be taken as April 30, 2014. This corresponds to the time-point when the last enrolled patient in the phase IIb part completed 12 cycles of treatment.

3.3 Definition of analysis sets

3.3.1 Phase Ib part

Safety Set: The safety set includes all patients who received at least 1 dose of any 1 compound of the study treatment.

MTD-determining set: consists of all patients of the safety set who either received sufficient study treatment as defined in the minimum exposure criteria in cycle 1 (patients need to have 100% of the planned dose of each compound, (as shown in the table below) and had sufficient safety evaluations or discontinued due to DLT in Cycle 1. Patients who do not meet these minimum safety evaluation requirements in cycle 1 will be regarded as ineligible for the MTD-determining set. From a programming point, a patient will be considered to have sufficient safety evaluations if he or she has information on vital signs and/or lab assessments taken during cycle 1. The information on whether a patient experienced a DLT during cycle 1 will be taken from the 'End-Of-Cycle' page for the first cycle.

Table 3-1 Minimum exposure criteria (Cycle 1)

Compound	Scheduled doses	Minimum exposure criterion
PAN	6	6
5-Aza	7	7

Full analysis set: This will be the same as the safety set.

PK set: consisted of all patients with at least 1 evaluable PK profile of PAN.

3.3.2 Phase IIb part

Safety Set: The safety set includes all patients who received at least one dose of any one component of the study treatment. Patients in the safety set will be analyzed as treated. The "as treated" information will be taken from the IVRS medication package that was actually dispensed. . However, patients who are randomized to the PAN+5-Aza group, and have not taken a non-zero dose of PAN as per the DAR panel, at the time of data cutoff, will be reported under the 5-Aza group for analyses based on the safety set.

Patients who have been randomized but did not take at least one dose of any component of study treatment will not be included in the safety set.

Full analysis set: consists of all patients who were randomized to one of the two treatment arms. Following the intent-to-treat (ITT) principle, the patients in the FAS will be analyzed in the treatment group they were assigned to at randomization. The randomized treatment information will be taken from the IVRS patient randomization listing.

3.4 Population and grouping for the analyses

For all safety analyses in phase Ib/IIb, the safety set will be used. The FAS will be used for all efficacy analyses, as well as, for analysis of patient disposition, demography and baseline characteristics in phase Ib/IIb. For the determination of the MTD in phase Ib part, the MTD-determining set will be used. For the analysis of PK data in phase Ib part, the PK set will be used. The MTD determining set and the PK set are defined and applicable only for the phase Ib part.

3.5 Protocol deviations

All protocol deviations and patient classification rules as specified in the VAP module 3, will be finalized before database lock.

Protocol deviations will be , summarized and listed by initial dose group of PAN for the phase Ib part and by treatment arm for the phase IIb part.

3.6 Concomitant therapy

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) besides the study treatment, that were intentionally administered to a patient preceding or coincident with the study assessment period.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List to allow for categorization by preferred term. In addition to categorizing medication data by preferred term, drugs are classified according to their ATC classification in order to present and compare how they are being utilized. The ATC classification allows for the summary of medications by a high-level common drug class.

Concomitant medications and significant non-drug therapies taken concurrently with the study treatment will be listed and summarized by ATC class, preferred term and initial dose group of PAN by means of frequency counts and percentages. These summaries will include medications starting on or after the start of study treatment or medications starting prior to the start of study treatment and continuing after the start of study treatment.

Any prior concomitant medications or significant non-drug therapies starting and ending prior to the start of study treatment will be listed.

3.6.1 Concomitant medications with specific impact on the analysis

3.6.1.1 Further anti-neoplastic therapy

Patients who take additional anti-neoplastic therapy before discontinuing study treatment (i.e., anti-neoplastic therapy other than study treatment) will be identified as protocol deviations. Their efficacy data will be censored so that response assessments made after the first intake of an anti-neoplastic drug will not be included in analyses.

3.7 General statistical methodology

3.7.1 Baseline comparability

Baseline variables refer to characteristics of patients at the start of a study.

As this is not a comparative study, no assessment of baseline comparability will be done. Instead, baseline characteristics will be described by initial dose group of PAN in the phase Ib part and by treatment group in the phase IIb part.

3.7.2 Multiple assessments within post-baseline visits

If there are multiple measurements/samples within the same post-baseline visit, the last measurement/sample within the visit (sorted by date and as available by time or repeat measurements) will be used in the analysis by visit or overall. For any analysis regarding outlier or abnormal assessments, all post-baseline values will be included (scheduled, unscheduled, repeat). For any other analyses, only scheduled visits will be included. This applies to quantitative and qualitative variables. For composite assessments, these rules apply for the complete sample (e.g., bone marrow differential counts, differential blood counts). It is not allowed to mix these variables across samples.

3.7.2.1 12-lead ECG assessments

The visit day recorded in the database will be used as the day of ECG. For all patients, a minimum of 3 ECGs are measured at all assessment time points except at screening (one ECG only). If any patient has more than 1 measurement at a specific time point, the average of all available measurements will be used for the analysis of change from baseline. Unscheduled measurements will be included for analysis of outliers and listings.

3.7.3 Center pooling

All study centers will be combined for the analysis unless otherwise specified. Due to expected small size of centers, no center effect will be assessed. However, number of patients will be summarized by analysis set, center and country.

3.7.4 1-sided vs. 2-sided test

No statistical testing will be performed.

3.7.5 Between group comparisons

Not applicable.

3.7.6 Conversion factors

A month will be calculated as (365.25 / 12) = 30.4375 days.

For the conversion of laboratory values measured in units as used by local laboratories to SI units, standard Novartis' conversion factors will be used.

3.8 Implementation of efficacy criteria

Response evaluation will be performed according to the Cheson (2003, 2006) criteria as implemented in the Clinical Study Protocol Post-text supplement 1.

4 Statistical methods used in reporting

4.1 Background and demographic characteristics

The full analysis set will be used for all baseline and demographic summaries and listings.

4.1.1 Basic demographic and background data

All demographic and background data will be listed in detail. Qualitative data will be summarized by means of contingency tables and quantitative data will be summarized by appropriate descriptive statistics (mean, standard deviation, median, minimum, and maximum) Data will be reported by the initial dose group of PAN for the phase Ib part and by treatment group for the phase IIb part. The following variables will be summarized:

- Age [years], (< 65 years, ≥ 65 years)
- Height [cm]
- Weight [kg]
- Sex (male/ female)
- Race (Caucasian/ Black/ Asian/ Native American/ Pacific Islander/ Other)
- Ethnicity (Hispanic/latino/ Chinese/ Indian (Indian subcontinent)/ Japanese/ Mixed ethnicity/ Other)
- ECOG status (0/ 1/ 2/ >2)
- Respiratory rate [/min]
- Body temperature [°C]
- BMI [kg/m^2]
- Body surface area (BSA) [m^2]
- Transfusion-dependent (yes/ no)
- Number of patients by disease (MDS/ AML/ CMML)

4.1.2 Protocol eligibility criteria

Protocol eligibility criteria on CRFs will be summarized and listed by initial dose group of PAN for the phase Ib part and by treatment group for the phase IIb part.

4.1.3 Diagnosis and characteristics of disease

Summary statistics will be tabulated (by initial dose group of PAN for the phase Ib part and by treatment group for the phase IIb part) for diagnosis and characteristics of AML, CMML and MDS and depending on the data collected on the CRF include the following:

- WHO classification of MDS at initial diagnosis
  - Refractory anemia (RA)
  - Refractory anemia with ringed sideroblasts (RARS)
  - Refractory cytopenia with multilineage dysplasia (RCMD)
  - Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)
  - Refractory anemia with excess blasts-1 (RAEB-1)
  - Refractory anemia with excess blasts-2 (RAEB-2)
  - Myelodysplastic syndrome , unclassified (MDS-U)
- FAB classification of MDS at initial diagnosis
  - Refractory anemia (RA)
  - Refractory anemia with ringed sideroblasts (RARS)
  - Refractory anemia with excess blasts (RAEB)
- Cytogenetics of MDS at initial diagnosis (Not done/ Favorable/ Intermediate/ Unfavorable)
- MDS IPSS risk category (low/ intermediate-1/ intermediate-2/ high)
- MDS disease status at enrolment (previously untreated/ previously treated)
- WHO classification of AML at initial diagnosis
  - AML with multilineage dysplasia (BM blasts 21-30%)
    - Following MDS
    - Following MDS/MPD
    - Without antecedent MDS or MDS/MPD but dysplasia in at least 50% of cells in 2 or more myeloid lineages
    - Other
  - AML (BM blasts > 30%)
- FAB classification of AML at initial diagnosis
  - M0: Minimally differentiated acute myeloblastic leukemia
  - M1: Acute myeloblastic leukemia, without maturation
  - M2: Myeloblastic with granulocytic maturation
  - M3: Acute promyelocytic leukemia
  - M4: Acute myelomonocytic leukemia
  - M4eo: Myelomonocytic together with bone marrow eosinophilia
  - M5: Acute monoblastic leukemia without differentiation or acute monocytic leukemia

  - M6: Acute erythroid leukemia including erythroleukemia and very rare pure erythroid leukemia
  - M7: Acute megakaryoblastic leukemia
  - Acute myeloid leukemia, not otherwise categorized
  - Other
- time since initial diagnosis of AML until start of treatment (phase Ib part) or randomization date (phase IIb part) and by categories:
  - < 1 month
  - ≥ 1 month to ≤ 3 months
  - 3 months to ≤ 6 months
  - months to ≤ 12 months
  - 12 months to ≤ 24 months
  - 24 months
  - unknown
- duration of first CR to AML
  - refractory
  - ≤ 6 months
  - > 6 month to ≤ 12 months
  - > 12 months to ≤ 24 months
  - > 24 months
  - unknown
- AML disease status (previously treated/ previously untreated)
- Cytogenetics AML (favorable/ intermediate/ poor/ not done)
- WHO classification of CMML
  - Chronic myelomonocytic leukemia (CMML) Myelodysplastic disease (WBC < 13 x 10^9/L, BM blasts 10-29%)
  - Chronic myelomonocytic leukemia (CMML) Myeloproliferative disease (WBC ≥ 13 x 10^9/L)
- CMML status at enrolment (previously untreated/ previously treated).
- Time since diagnosis [months] (all diseases)

4.1.4 Medical history

Medical history and ongoing conditions, including leukemia-related conditions and symptoms will be summarized and listed. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class and preferred term (by initial dose group of PAN for the phase Ib part and by treatment group for the phase IIb part). Medical history/current medical conditions are coded using the Medical dictionary for regulatory activities MedDRA terminology.

4.1.5 Prior anti-neoplastic therapy

Prior anti-neoplastic therapy will be listed for medications, radiotherapy and surgeries.

The number and percentage of patients receiving any prior anti-neoplastic therapy, surgeries, radiotherapy, and prior anti-neoplastic medications will be summarized.

4.1.6 Other

All data collected at baseline, including source of patient referral, childbearing potential, pregnancy test results, cytogenetics, [redacted], will be listed (by initial dose group of PAN for the phase Ib part and by treatment group for the phase IIb part).

Demographic information on screening failures will be listed together with the reason for screening failure.

4.2 Protocol deviation summaries

The number and percentage of patients in the FAS with any protocol deviation will be tabulated by the deviation category (as specified in the Validation and Analysis Plan [VAP] documents). Protocol deviations will also be listed. The tabulation and listing will be done by the initial dose group of PAN for patients in the phase Ib part, and by treatment group for patients in the phase IIb part.

4.3 Groupings for Analysis

The number and percentage of patients in each analysis set (definitions are provided in Section 2.3) will be summarized by initial dose group of PAN for the phase Ib part and by treatment group for the phase IIb part).

4.4 Patient disposition

The full analysis set will be used for the patient disposition summaries.

The following frequencies will be provided by initial dose group of PAN for the phase Ib part and by treatment group for the phase IIb part:

- Number (%) of patients who were enrolled
- Number (%) of patients who are still in the treatment phase at the cut-off date
- Number (%) of patients who discontinued the study treatment (based on 'End of Treatment' page)
- Number of patients (%) by primary reason for treatment discontinuation (based on 'End of Treatment' page: AE(s)/ Abnormal laboratory value(s)/ Abnormal test procedure result(s)/ Patient withdrew consent/ Lost to follow-up/ Administrative problems/ Death/ Disease progression/ Protocol deviation/ Reason missing)
- Number (%) of patients who entered the post-treatment evaluation phase (based on 'End of Treatment' page
- Number (%) of patients who entered the post-treatment evaluation and completed the study (based on 'Study Evaluation Completion' page)
- Number (%) of patients who entered the post-treatment evaluation and who discontinued the study (based on 'Study Evaluation Completion' page)

- Reasons for discontinuation from the post-treatment evaluation phase (based on 'Study Evaluation Completion' page: Patient withdrew consent/ Lost to follow-up/ Administrative problems/ Death/ New cancer therapy/ Disease progression/ Protocol deviation/ Follow-up phase completed/ Reason missing).

4.5 Follow-up

To describe the maturity of data and quality of follow-up, the following summaries on the follow-up of patients will be provided by treatment group for the phase IIb part.

Median duration of follow-up described as the duration of time elapsed from the first visit (per the visit record) of the median patient enrolled to date of data cut-off.

Time elapsed from last contact (or death) of patient to date of data cut-off summarized by the following interval times.

- 0 to <1 month
- ≥1 to <3 months
- ≥3 to < 6 months
- ≥6 to < 12 months
- ≥12 months

The **date of last contact** is defined as the last date the patient was known to be alive as derived from different CRF pages as described below.

4.6 Last contact date

The last contact date should be derived as the latest date on or before the data cut-off date from the dates listed in the 1st column of Table 4-1. For each of the sources specific conditions (2nd column of Table 4-1) have to be fulfilled to ensure that there was true contact with the patient.

No additional dates are allowed to be used, e.g. dates coming from concomitant medications, QoL, ECG, etc. The rationale for excluding those additional potential sources is the following:

- Use of a transparent and easy to implement approach that can be standardized across most of the studies.
- The risk of disregarding important information is low since the last contact date is expected to be obtained from the main sources listed in Table 4-1.

Table 4-1 Last contact date data sources

Source data	Conditions
Date of Randomization	No Condition
Last contact date/last date patient was known to be alive from Survival Follow-up page	- Patient status is reported to be alive. **- Do not use if patient status is reported unknown.**
Start/End dates from further antineoplastic	Non-missing medication/procedure term.

Source data	Conditions
therapy	
Start/End* dates from drug administration record	Non-missing dose. Doses of 0 are allowed.
End of treatment date from end of treatment page	No condition.
Efficacy (any specific assessment) assessment date	Evaluation is marked as 'done'.
Laboratory/PK collection dates	Sample collection marked as 'done'.
Vital signs date	At least one parameter value
Performance Status date	Non-missing performance status

4.7 Study treatment and duration of study treatment exposure

All summaries mentioned below will be presented (in addition to groupings mentioned below) by initial dose group of PAN for the phase Ib part and by treatment group for the phase IIb part. Duration of study treatment exposure [days] will be summarized overall, and by compound. . The cumulative dose [mg], dose intensity (DI) [mg/day] and relative dose intensity (RDI) [%] will be summarized by compound. The number of patients who have dose reductions or interruptions and the reasons will be summarized.

Listings of all doses of the study treatment, along with dose change reasons, will be produced by compound.

The safety set will be used for all summaries and listings of study treatment.

4.7.1 Duration of study treatment exposure

In summarizing the duration of exposure to study treatment and study treatment component the following working definitions and conventions will be used.

Duration of study treatment exposure

Duration of exposure (days) = [(date of last administration of study treatment) – (date of first administration of study treatment) + 1 day]

Duration of study treatment component exposure

Duration of exposure to any single component of study treatment will be calculated as

Duration of exposure (days) = [(date of last administration of study treatment component) – (date of first administration of study treatment component) + 1 day]

The date of last administration of study treatment is taken from CRF treatment completion page 'last dose taken'. For the date of last administration of the treatment component, the DAR page must be used.

The calculation of 'duration of exposure' does not consider the potential 'lagging effect' from the last dose.

The duration includes the periods of temporary interruption (of any component of the study treatment for any reason). 'Date of last administration of study drug /component' and 'date of first administration of study drug /component' is defined in Section 2.1. For patients who did not take any study treatment the duration of exposure is defined as zero days.

The following categories for exposure to study treatment (by component) will be analyzed:

- < 1 week
- 1 week to < 3 weeks
- 3 weeks to < 6 weeks
- 6 weeks to < 9 weeks
- 9 weeks to < 12 weeks
- ≥ 12 weeks

4.7.2 Cycle definition

Cycle length will be calculated based on the cycle panel for this study.

Using cycle panel (except last cycle),

Cycle length= (date of day 1 of the next cycle – date of day 1 of the current cycle).

The actual length of a treatment cycle might differ from the scheduled length:

- In case of Adverse Events which led to a dose delay, the duration of the cycle might be longer than the scheduled length.
- In case a patient was withdrawn from the study, the length of the last treatment cycle might be shorter than the scheduled length

4.7.2.1 Last cycle

Since patient can discontinue the study early, last cycle may not be a complete cycle for treatment. The calculation of last cycle length needs special attention, i.e.,

Last Cycle Length= [(date of last administration of study treatment component +X) – (day 1 of the last cycle date) + 1].

where X is the number of days remaining to complete the exposure time of the last dose of the study treatment component or the number of days from last administered dose to the next planned dose. This can be better understood by referring to the dosing schedule for the phase IIb part given in Figure 4-1 (note: dosing schedule for the phase Ib part would follow the investigational arm of the phase IIb part). The dose is given on days marked by the dark filled-in slots. X would equal the number of unfilled slots between the filled-in slot that marks the last dose and the next filled-in slot that would mark the next scheduled dose.

For PAN:

If last dose is given on day 1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 13, 14 of the cycle, X = 1

If last dose is given on day 5, 12 of the cycle, X = 2

If last dose is given on day 15 to 27 the cycle, X = 28 – day of last dose

If last dose is given on day 28 and beyond, X = 0

For 5-Aza:

If last dose is given on day 1 through day 6 of the cycle, X = 0.

If last dose is given on day 7 to day 27 of the cycle, X = 28 – day of last dose.

If last dose is given on day 28 and beyond, X = 0

The special handling of the last cycle length is to carefully calculate dose intensity. This is different from the purpose of calculating 'duration of exposure' where 'last dose lagging effect' is not included.

Figure 4-1 Treatment schedule (Phase IIb part)

Investigational arm:

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
panobinostat			■		■			■		■		■			■													
5-Aza (Vidaza®)	■	■	■	■	■	■	■																					

Active control arm:

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
5-Aza (Vidaza®)	■	■	■	■	■	■	■																					

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
5-Aza (Vidaza®)	■	■	■	■	■	■	■																					

4.7.3 Partial dates

Partial dates will be listed as partial dates. The general approach is to impute partial dates only when further analysis is required.

As a common rule, whenever an imputation is implemented, the imputed date needs to be in the reasonable range of the event. In general, no imputation will be made when the year is missing (exceptions if any will be described in RAP Module 8). In case the imputation process results in a date that is not plausible given known key study dates, the imputed date is to be replaced with a date that is aligned with those known key dates. As an example, when imputing an AE start date results in a date prior to start of study treatment then the AE start date will be set to the study treatment start date. Or for example, if a date is known to be within the trial period and imputation makes it after the last known contact date, the last known contact date will be used.

The details for the different scenarios will be specified in RAP module 8.

4.7.4 Cumulative dose

Cumulative dose [mg] is defined as the total dose given during the study treatment exposure. For patients who did not take any drug the cumulative dose is by definition equal to zero.

4.7.5 DI and RDI

The following DI or planned DI (PDI) calculations apply for both PAN and 5-AZA. For 5-AZA, where the dose was given based on BSA, the cumulative dose or the total planned dose may need to be divided by BSA, in the calculation of DI or PDI depending on how actual dose information is collected in the database. If the reported actual dose is already adjusted for BSA (e.g. the unit is mg/m^2), then adjustment for BSA is not needed. It should be noted

that if RDI alone is being reported, the calculation of BSA (which appears in both the numerator and the denominator of the formula for RDI and hence cancels out), is not necessary. If BSA is not collected in the CRF then the weight provided at Day 1 of each cycle will be used to calculate the actual BSA (if needed) for each cycle as:

Body Surface Area (Gehan and George):

BSA [m2] =234.94*(height (cm)**0.422)*(weight(kg)**0.515)/10000.

4.7.6 Dose intensity over study period

PAN and 5-AZA

Dose intensity (DI) for patients with non-zero duration of exposure is defined as follows:

$$\text{DI}\ [\text{mg/day}] = \frac{\text{Cumulative dose}\ [\text{mg}]}{\sum_{i=1}^{k} (\text{actual cycle lengths})_i\ [\text{day}]}$$

and i =1,2,3,…,k are the indices for the cycle.

For patients who did not take any drug the DI is by definition equal to zero.

Note: $\sum_i (\text{actual cycle length})_i$ may not be equal to the duration of the study treatment exposure.

Planned dose intensity (PDI) for patients with non-zero duration of exposure is defined as follows:

1. Last cycle length is shorter as or equal to the planned length

$$\text{PDI}\ [\text{mg/day}] = \frac{\text{Total planned dose}\ [\text{mg}]}{\sum_{i=1}^{k-1} (\text{Planned cycle lengths})_i + \text{actual last cycle lentgh}\ [day]}$$

i =1,2,3,…,k are the indices for the cycle. k is the actual total number of cycles

2. Last cycle length is longer than planned

$$\text{PDI}\ [\text{mg/day}] = \frac{\text{Total planned dose}\ [\text{mg}]}{\sum_{i=1}^{k} (\text{Planned cycle lengths})_i\ [\text{day}]}$$

i =1,2,3,…,k are the indices for the cycle. k is the actual total number of cycles

For patients who did not take any drug the PDI is by definition equal to zero.

Relative dose intensity (RDI) is defined as follows:

RDI [%] = DI [mg/day] / PDI [mg/day] * 100

The definition and analysis will be applicable only for patients with non-zero PDI.

Relative dose intensity will be summarized by compound. This will be done by initial dose group of PAN for the phase Ib part and by treatment group for the phase IIb part.

The number of patients who have dose reductions or interruptions, and the reasons, will be summarized by initial dose group of PAN for the phase Ib part and by treatment group for the phase IIb part . The instructions given to sites regarding completion of dose administration records are provided in the appendix and should be referred to when developing the program code or logic as appropriate.

A continuous dose recording scheme (whereby a new entry is made only when there is a change/delay/interruption to the planned dose and schedule) is used for this study. For the purpose of dose intensity calculations, the following algorithm will be used to assign doses:

- **For 5-Aza:** a dose will be assigned daily from start to end date

- **For PAN:**
    - **For records with a dose starting on any of the protocol days (3,5,8,10,12,15)** => doses will be assigned on the days as per planned.
        - e.g. if PAN started on C1D3 and ended on C1D14, 5 doses will be assigned (on days 3,5,8,10, and 12)
    - **For records with doses starting on a non-protocol day** => a dose will be assigned every other day, upto a maximum of 6 doses per cycle.

4.8 Concomitant therapy

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) besides the study treatment, which were intentionally administered to a patient preceding or coincident with the study assessment period.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List to allow for categorization by preferred term. In addition to categorizing medication data by preferred term, drugs are classified according to their ATC classification in order to present and compare how they are being utilized. The ATC classification allows for the summary of medications by a high-level common drug class.

Concomitant medications and significant non-drug therapies taken concurrently with the study treatment will be listed and summarized by ATC class, preferred term.This will be done by the initial dose group of PAN in the phase Ib part and by treatment group in the phase IIb part. Separate summaries and listings will be generated for concomitant medications started prior to the start of study treatment, and those started after the start of study treatment.

The safety set will be used for all concomitant medication summaries and listings.

4.8.1 Concomitant medications with specific impact on the analysis

4.8.1.1 Further anti-neoplastic therapy

Patients who take additional anti-neoplastic therapy before discontinuing study treatment (i.e., anti-neoplastic therapy other than study treatment) will be identified as protocol deviations. Their efficacy data will be censored so that response assessments made after the first intake of an anti-neoplastic drug will not be included in analyses.

4.9 Primary safety variable

The primary safety variable is the incidence of DLT as observed in the phase Ib part.

4.9.1 Analysis of the primary safety variable

There is no formal testing of statistical hypotheses. An adaptive Bayesian logistic regression model with overdose control will be used to guide the dose-escalation procedure. This model will be used to estimate probabilities for toxicity categories (underdosing, target toxicity, excessive and unacceptable toxicity) as taken from the posterior distribution. For details refer to the Post-text supplemental 1. The MTD-determining set is the primary analysis set.

The probability for each of the toxicity classes will be provided for the determined MTD in terms of simulations as obtained by the BLRM.

4.9.2 Sensitivity and other supportive analyses

None are planned.

4.10 Safety evaluation

The assessment of safety will be based mainly on the frequency of AEs and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g. electrocardiogram, vital signs, special tests) will be considered as appropriate. Unless otherwise mentioned, all summary safety outputs (including deaths, adverse events, laboratory values, vital signs, ECGs, and ECOG performance status) will be reported by initial dose group of PAN for the phase Ib part and by treatment group for the phase IIb part, in addition to other groupings specified for that analysis.

All safety outputs will use the safety set. The safety summary tables will include only assessments collected no later than 28 days after study treatment discontinuation. All safety assessments will be listed and those collected later than 28 days after study treatment discontinuation will be flagged.

4.10.1 Adverse events

Coding of AEs

AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology version 16.0 or later.

Grading of AEs

AEs will be assessed according to the Common Terminology Criteria for AEs (CTCAE version 3.0 or later). If CTCAE grading does not exist for an AE, grades 1 – 4 corresponding to the severity of mild, moderate, severe, and life-threatening will be used. CTCAE grade 5 (death) is not be used in studies; rather, this information will be collected in the "End of Treatment" or "Study Completion Evaluation" CRF pages.

Reporting of AEs

AE summaries will include all treatment emergent AEs starting on or after Study Day 1 (i.e. on or after the day of the first intake of study treatment) and starting no later than 28 days after study treatment discontinuation. All AEs will be listed. AEs starting prior to Study Day 1 and AEs starting later than 28 days after study treatment discontinuation will be flagged in the listings.

A patient with multiple occurrences of an AE will be counted only once in the respective AE category.

AE summaries will be presented by primary system organ class, preferred term, and maximum CTC grade. A patient with multiple CTC grades for an AE category will be summarized under the maximum CTC grade recorded for the event. In the summaries presented by grade, all AEs will be pooled regardless of whether they are CTC gradable or not, i.e. regardless of whether the question "CTCAE" on the AEs CRF is answered 'Yes' or 'No'.

The frequency of all CTC grades and grade 3 and 4 AEs will be summarized separately. Any information collected (e.g. CTC grades, relatedness to study treatment, action taken etc.) will be listed as appropriate.

Summaries of AEs with suspected relationship to study treatment will be provided.

Deaths reportable as serious AEs (SAEs) and non-fatal SAEs will be listed by patient and tabulated.

4.10.2 AE summaries

The following incidences of AE summaries will be produced:

- AEs, regardless of study treatment relationship by primary system organ class and preferred term
- AEs with suspected relationship to study treatment by primary system organ class, preferred term
- AEs with an overall incidence rate of 10%, regardless of study treatment relationship by primary system organ class and preferred term
- CTC grade 3 or 4 AEs, regardless of study treatment relationship by primary system organ class and preferred term
- CTC grade 3 or 4 AEs with suspected study treatment relationship by primary system organ class and preferred term
- Deaths up to 28 days after end of treatment by primary system organ class and preferred term

- Deaths after 28 days after end of treatment by primary system organ class and preferred term
- Serious AEs, regardless of study treatment relationship, by primary system organ class and preferred term
- AEs leading to study treatment discontinuation, regardless of study treatment relationship, by primary system organ class and preferred term
- AEs requiring dose adjustment or study-treatment interruption, regardless of study treatment relationship, by primary system organ class and preferred term
- AEs requiring additional therapy, regardless of study treatment relationship, by primary system organ class and preferred term.

4.10.3 Clinical notable AE

Specific groupings of clinically notable AEs will be considered and the number of patients with at least 1 AE within each grouping will be reported. Such groups consist of AEs for which there is a specific clinical interest in connection with PAN (i.e. where PAN may influence a common mechanism of action responsible for triggering them) or which are similar in nature (although not identical). The groups are defined as per Table 4-2 below and in RAP Module 8.). These groupings are based on standardized MedDRA queries and Novartis MedDRA queries. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit to the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad.

Table 4-2 Clinical notable AE

Clinically notable adverse events grouping	Source
Identified risks	
QT prolongation	SMQ - Broad
Myelosuppression	
Haematopoietic erythropenia	SMQ – Broad
Haematopoietic cytopenias	SMQ – Broad
Haematopoietic leukopenia	SMQ – Broad
Haematopoietic thrombocytopenia	SMQ - Broad
Hemorrhage	SMQ - Narrow
Hepatic dysfunction	SMQ - Broad
Renal dysfunction	SMQ - Broad
Severe infections	
Pneumonia	NMQ - Broad [selected relevant PTs for infectious pneumonia]
Sepsis	NMQ - Broad [selected relevant PTs for infectious sepsis]
Potential risks	

Clinically notable adverse events grouping	**Source**
Acute pancreatitis	NMQ - Broad [SMQ acute pancreatitis, excluding PTs for non-specific symptoms]
Cardiac failure	SMQ - Narrow
Hypothyroidism	SMQ - Broad
Interstitial lung disease	SMQ – Broad
Ischemic colitis	SMQ – Broad
Ischemic heart disease	SMQ - Narrow
Reactivation of Hepatitis B infection	NMQ – Broad [selected PTs including relevant serology tests]
Tachyarrhythmias	NMQ - Broad [SMQ tachyarrhythmias (including supraventricular and ventricular) and additional selected PTs]
Venous Thromboembolism	SMQ - Narrow
Pericardial effusion	NMQ – Broad **[**selected relevant PTs for pericardial effusion]
Further	
Peripheral neuropathy	SMQ
Asthenia / fatigue	PT

A summary of these clinical notable AEs will be provided by treatment group for the phase IIb part.

4.10.4 Laboratory data

On analyzing laboratory assessments, data from all sources (central and local laboratories) will be combined. The summaries will include all laboratory assessments collected no later than 28 days after study treatment discontinuation. All laboratory assessments will be listed and those collected later than 28 days after study treatment discontinuation will be flagged in the listings.

Laboratory data will be classified into CTC grades according to the NCI CTCAE. A severity grade of 0 will be assigned when the value is within normal limits. In the unlikely case when a local laboratory normal range overlaps into the higher (i.e. non-zero) CTC grade, the laboratory value will still be taken as within normal limits and assigned a CTC grade of zero.

In case the lab presented blood counts as percentage of the total white blood cell count, the absolute blood counts will be derived. Both the percent blood count and the total white blood cell count have to be taken from the same blood sample.

For all the differential counts, percentages will be converted to absolute values, if necessary, as

$$Absolute\ value = (percentage * WBC) / 100$$

In order to derive the corresponding **absolute normal range,** the following scenarios (depending on the availability of the % range and the absolute range for the differential) will be considered:

- **1st scenario: % range missing and absolute range missing**

Use pre-defined normal range reported in the Merck manual

- **2nd scenario: % range missing and absolute range NOT missing**

Use the absolute range provided by the site

- **3rd scenario: % range NOT missing and absolute range NOT missing**

Use the absolute range provided by the site

- **4th scenario: % range NOT missing and absolute range missing**

Approved rule: the % normal limits (i.e. LLN and ULN) are divided by 100 and multiplied by the corresponding normal limits of WBC count, e.g. for neutrophils (NEU):

- LLN for NEU count = (LLN for WBC count) * (LLN for NEU % / 100)
- ULN for NEU count = (ULN for WBC count) * (ULN for NEU % / 100**)**

The following summaries will be produced for the laboratory data (by laboratory variable):

- Number and percentage of patients with worst post-baseline CTC grade (regardless of the baseline status). Each patient will be counted only for the worst grade observed post-baseline.
- Shift tables using CTC grades to compare baseline to the worst post-baseline value will be produced for hematology and biochemistry laboratory parameters with CTC grades.
- For laboratory parameters where CTC grades are not defined (eg. thyroid hormones), shift tables to the worst post-baseline value will be produced using the low/normal/high classifications based on laboratory reference ranges.

The number of granulocytes blood count will be calculated as sum of the neutrophil, basophil and eosinophil blood count.

The following listings will be produced for the laboratory data:

- Listing of patients with laboratory values outside the laboratory reference ranges with values flagged to show the corresponding CTC grades and the classifications relative to the laboratory reference ranges
- Listing of all laboratory data with values flagged to show the corresponding CTC grades and the classifications relative to the laboratory reference ranges.

4.10.5 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The variables collected are:

- Weight [kg]
- Body temperature [°C]
- Heart rate [beats per minute]
- Systolic and diastolic blood pressure [mmHg]
- Respiratory rate [breaths per minute].

Patients with clinically notable vital sign abnormalities will be listed and assessments collected later than 28 days after study treatment discontinuation will be flagged in the listings. The criteria for clinically notable abnormalities are depicted in Table 4- and Table 4-4.

Table 4-3 Clinically notable elevated values

Variable	Criteria
Systolic BP	ǂ 180 mmHg and an increase ǂ 20 mmHg from baseline
Diastolic BP	ǂ 105 mmHg and an increase ǂ 15 mmHg from baseline.
Body temperature	ǂ 39.1°C (102.3°F)
Weight	increase from baseline of ǂ 10%
Heart rate	ǂ 120 bpm with increase from baseline of ǂ 15 bpm
Respiratory rate	≥ 30 breaths per minute

Table 4-4 Clinically notable below normal values

Variable	Criteria
Systolic BP	£ 90 mmHg and a decrease ǂ 20 mmHg from baseline
Diastolic BP	£ 50 mmHg and a decrease ǂ 15 mmHg from baseline
Body temperature	£ 35°C (95°F)
Weight	decrease from baseline of ǂ 10%
Heart rate	£ 50 bpm with decrease from baseline of ǂ15 bpm
Respiratory rate	≤ 10 breaths per minute

4.10.6 Handling of missing values

Any post-baseline AE with a missing grade will be substituted by grade 4.

4.10.7 ECG

Definition of baseline and post-baseline QTcF

4.10.7.1 Baseline definition

Quantitative ECG:

Baseline is defined as an average of all pre-dose ECGs performed on Cycle 1 Day 1 if available. Otherwise, the average of all pre-dose ECG measurements taken on most recent day prior to the start of study treatment within the protocol-defined time window is considered as baseline. Unscheduled visits are included.

Note: if the unscheduled visits have been done on Cycle 1 Day 1 but without time, these assessments will not be included in baseline derivation.

Qualitative ECG:

Baseline is defined as the last assessment (or set of assessments) prior to the first dose of study treatment within the protocol-defined time window. Unscheduled visits are included.

4.10.7.2 Post-Baseline value

All measurements taken after first dose of study treatment will be considered as post baseline.

4.10.7.3 Population for analysis

Quantitative ECG:

Patients will be considered evaluable (included in "Total") for outlier analysis if they are at risk at baseline and have at least one post-treatment ECG measurement. For change from baseline analyses they have to have at least one baseline ECG measurement and one post-baseline measurement.

A patient is considered at risk at baseline for the respective outlier category, if the baseline of this patient is:

- Missing or ≤450 msec for category "New > 450 and ≤ 480 ms"
- Missing or ≤480 msec for category "New > 480 and ≤ 500 ms"
- Missing or ≤500 msec for category "New of > 500 ms"

Qualitative ECG

A patient is considered at risk for each individual finding if the baseline of the patient is:

- Missing or with baseline being normal for that particular finding.

4.10.7.4 QTcF prolongation summary

Notable abnormalities will be summarized for the following:

- an increase of 30- 60 ms compared to baseline
- an increase of > 60 ms compared to baseline
- patients with any value of > 450 ms and ≤ 480 ms
- patients with any value of > 480 ms and ≤ 500 ms
- patients with any value of > 500 ms

For outlier abnormalities, similar analysis will be made excluding missing baseline (optional).

For the following Quantitative ECG summaries, the patients with baseline and with at least one post baseline value will be included.

4.10.7.5 Qualitative ECG summary

Summary of newly occuring of All qualitative ECG findings will be reported:

- Including missing baseline values

- Excluding missing baseline values (optional)

4.10.8 ECOG performance status

ECOG PS scale is used to assess physical health of patients, ranging from 0 (most active) to 5 (least active):

Table 4-5 ECOG performance scale

Score	Description
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

Shift tables comparing the baseline performance status with the worst result during study will be summarized.

4.11 Efficacy analysis

4.11.1 Efficacy analysis for the phase Ib part

[redacted] Listing of the data on response variables as assessed by the investigator will be provided.

The best overall response as categorized by the criteria used and assessed by the investigator will be reported by patient. These assessments will be performed for all patients of the FAS and results will be presented per initial dose group of PAN in tabular form. Point estimates and 95% CIs according to Clopper-Pearson will be provided for best response based on the FAS.

4.11.2 Efficacy analysis for the phase IIb part

The primary efficacy endpoint will be the composite CR (CR or CRi or bone marrow CR) among all patients in the FAS.

The following efficacy endpoints will be considered.

- Clinical response for AML: CR, CRi, PR
- Clinical response for MDS/CMML: CR, bone marrow CR, PR and Hematologic Improvement (HI)

- 1-year survival rate
- Time to Progression (TTP)

No formal statistical test comparing the two arms will be done on any of the endpoints since the study was not powered to do that.

4.11.2.1 Clinical response for AML and MDS/CMML

Clinical responses will be summarized by treatment arm, overall and within disease type (i.e. AML or MDS/CMML). Percentage rates for the composite CR rate (CR or CRi or bone marrow CR), overall response rate (CR or CRi or bone marrow CR or PR) will be reported along with 95% confidence intervals for both arms. Exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated Clopper and Pearson 1934. Point estimates and confidence intervals for the difference in rates between the treatment arms will also be reported.

4.11.2.2 1-year survival rate

The 1-year survival rate will be obtained from the Kaplan-Meier analysis of overall survival, and its variance will be estimated by Greenwood's formula. Overall survival is defined as the time from date of randomization to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last contact. Patients not known to have died will be censored for 'Lost to follow-up' if the time between their last contact date and the analysis cut-off date is longer than 3 months and 2 weeks (104 days) during the first year after study evaluation completion, and longer than 6 months and 2 weeks (194 days), thereafter. This takes into account the fact that survival follow-up is every 3 months during the first year after completion of study evaluation, and every 6 months thereafter, and allows for a window of 2 weeks to accommodate reasonable delays in reporting.

4.11.2.3 Time to Progression (TTP)

Time to progression (TTP) is defined as the time from the date of randomization to the date of the first documented PD per investigator's assessment or death due to study indication. Time to progression will be analyzed by the Kaplan Meier method. The 25th, 50th (median), and 75th percentiles of the TTP and the 2-sided 95% CIs will be reported for both arms.

The event and censoring times for TTP are depicted in Table 4-6 below.

Table 4-6 Event and censoring dates used in TTP

	Situation	End-date	Outcome
A	No baseline assessment	Date of randomization	Censor
B	PD/relapse at scheduled assessment date or before next scheduled assessment	Date of PD/relapse	Event

	Situation	End-date	Outcome
C1	PD/relapse or death due to study indication after **exactly one** missing assessment	Date of PD/relapse/death	Event
C2	PD/relapse or death due to study indication after **two or more** missing assessments	Date of last adequate assessment before PD/relapse or death due to study indication (i.e. before the 2 or more missing assessments)	Censor
D	No PD/relapse/death due to study indication	Date of last adequate assessment[1]	Censor
E	Treatment discontinuation due to 'Disease PD/relapse' without documented PD/relapse, i.e. clinical PD/relapse based on investigator claim	N/A	Ignored
F	New anticancer therapy given[2]	Date of last adequate assessment before start of new anticancer therapy	Censor

[1] In case there is no adequate assessment, the end date is the date of randomization

[2] New anticancer therapy given without documented evidence of PD/relapse

4.11.3 Kaplan-Meier analysis

The analysis will be conducted via use of the SAS procedure LIFETEST where statement STRATA will include only the treatment group variable (*trt* in the example below). The TIME statement will include a variable with survival times (*survtime* in the example below) and a (right) censoring variable (*censor* in the example below) with one representing censoring:

```
PROC LIFETEST data=dataset TIMELIST=t1 t2 t3 METHOD=KM
CONFTYPE=LOGLOG;
     TIME survtime*censor(1);
     STRATA trt;
RUN;
```

- `survtime represents variable containing event/censor times`
- `censor represents censoring variable (1=censored, 0=event)`
- `trt represents treatment group variable`
- `t1, t2, and t3 represent the times at which survival estimates are to be reported, e.g. at 6 months, 9 months, and 1 year, say.`

4.11.4 Handling of missing values/discontinuations

Patients with best overall response of 'Unknown' by the respective efficacy criteria will be treated as non-responders in the calculation of the objective response rate in the full analysis set.

4.11.5 Transfusions

The total number of transfusion units by patient will be summarized by transfusion type indication (MDS/CMML, AML) and adjusted for the respective study period. This will be done by the initial dose group of PAN for patients in the phase Ib part and by treatment group for patients in the phase IIb part.

Number of units of transfusion of a specific type, for a patient, adjusted for the study period = (Total number of transfusion units of the specific type during the on-treatment period) / (on-treatment period in months)

where on-treatment period is defined as the following time interval:

> [date of first administration of study treatment; date of last administration of study treatment +28 days], i.e. inclusive of the lower and upper limits.

Transfusion-dependence will be assessed throughout the study. At baseline, a patient is to be considered transfusion-dependent if he/she has had an infusion of 4 or more units within the 8 weeks preceding treatment and 1 of those units was administered within 1 week immediately preceding treatment.

Post-baseline, a patient is considered not to be transfusion dependent until the start of the first transfusion notwithstanding transfusions during baseline. After start of treatment, a period of 7 days without any transfusion would define a patient as transfusion-independent.

Bone marrow assessment

Bone marrow variables as assessed by aspirate and/or biopsy will be listed. Differential cell counts as provided by aspirate will be listed by initial dose group of PAN in the phase Ib part and by treatment group in the phase IIb part. The last measurement per cycle will be used in

case of more than 1 assessment per cycle. In this case, all variables need to be from the same sample.

The differential cell counts include the following variables which will be listed:

Bone marrow aspirate

- Blasts [%]
- Promyelocytes [%]
- Metamyelocytes [%]
- Bands [%]
- Neutrophil [%]s
- Eosinophils [%]
- Basophils [%]
- Lymphocytes [%]
- Monocytes [%]
- Pronormoblasts/Proerythroblasts [%]
- Normoblasts/Erythroblasts [%]
- Plasma Cells [%]
- Other [%]

Bone marrow biopsy

- Blasts [%]

The following variables will be listed:

Bone marrow aspirate

- Was the specimen adequate for assessment (yes/ no)
  - if no: Dry tap/ hemodiluted/ other
- Are the differential results from smear/ touch imprints? (yes/ no)
- Auer rods present? (yes/no)
- Myeloid/ erythroid ratio
- Erythroid cells (absent/ decreased/ normal/ increased/ unknown, not done)
- Myeloid cells (absent/ decreased/ normal/ increased/ unknown, not done)
- Megakaryotype cells (absent/ decreased/ normal/ increased/ unknown, not done)
- Dysplasia (no/ yes)
  - If yes: erythroid/ myeloid/ megakaryocyte
- Cellularity done (yes/ no)
  - If yes:
    - aplastic
    - hypocellular (mild/ moderate/ severe)
    - normocellular
    - hypercellular (mild/ moderate/ severe)

- not available

Bone marrow biopsy

- Was the specimen adequate for assessment (yes/ no)
- Auer rods present? (yes/no)
- Cellularity done (yes/ no)
  - If yes:
    - aplastic
    - hypocellular (mild/ moderate/ severe)
    - normocellular
    - hypercellular (mild/ moderate/ severe)
    - not available
- Cellularity available? (yes/ no)
  - If yes:
    - %age of cellularity
- Megakaryotype cells (absent/ decreased/ normal/ increased/ unknown, not done)
- Dysplasia (no/ yes)
  - If yes: erythroid/ myeloid/ megakaryocyte

4.12 Handling of missing values/discontinuations

Patients with best overall response of 'Unknown' by the respective efficacy criteria will be treated as non-responders.

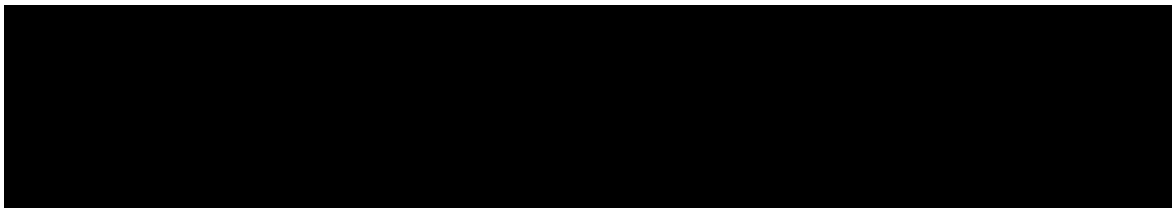
Missing values for CTC grading of AEs and laboratory values at baseline will be set to CTC grade 0.

4.13 Subgroup analysis

Not applicable.

4.14 Pharmacokinetic analyses

Plasma PAN levels collected during Cycle 1 of the phase Ib part of the study, on Days 4, 5, and 8 will be summarized by study day. Pre-dose levels of PAN (Cmin values) will be summarized at the study conclusion by study day and actual dose group of PAN. Values below the lower limit of quantification (LLOQ) of approximately 0.5 ng/mL will be reported as 0 ng/mL. Missing values will be labeled accordingly.



4.16 Interim analyses

Not applicable.

5 References

[Babb J, Rogatko A, Zacks S (1998)] Cancer Phase I clinical trials: efficient dose escalation with overdose control. Stat Med; 17: 1103-1120

[Cheson B, Bennet JM, Kopecky K, et al (2003)] Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. Journal of Clinical Oncology; 21(24):4642-4649

[Cheson BD, Greenberg PL, Bennet JM, et al (2006)] Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood (108):419-425

6 Appendix

A1 Instructions given to sites for completion of the DAR forms

1. GENERAL INSTRUCTIONS

- In general, the site must enter at least 1 record per cycle

- For patient WITHOUT dose delay/interruption, it is acceptable to have just one record for the cycle, with start date = day1/ 3 and end date = day 7/15 of the cycle for 5-Aza/Pan

- Planned dose is always the dose defined by the protocol (30 mg for Panobinostat for phase II, 75 mg/m2 for Vidaza). The most important is the first planned dose (C1D1 for 5-Aza and C1D3 for PAN). Note: for phase I, PAN could be from 10-60mg

2. DOSE CHANGE

Dose Change: To decide whether the dose was changed or not, it must be compared to previous non-zero dose received (and not to the planned dose)

Example:

Administration 1: Planned Dose 30 mg, Actual Dose 30 mg (Dose Change = No)

Administration 2: Planned Dose 30 mg, Actual Dose 20 mg (Dose Change = Yes)

Administration 3: Planned Dose 30 mg, Actual Dose 20 mg (Dose Change = No)

Administration 4: Planned Dose 30 mg, Actual Dose 0 mg (Dose Change = No – e.g. interruption, see below)

Administration 5: Planned Dose 30 mg, Actual Dose 20 mg (Dose Change = No)

3. DOSE DELAY

There are two situations to be considered in this study:

- Situation 1: Delay of a cycle (duration>28 days)

If the cycle is >28 days, Day 29 to the end of the cycle will be considered as dose delay and one record with 0 dose should be entered

Example: cycle start date is 1-April-2013 and end of cycle is 5-May-2013, 3 records should be entered:

a. For 5-Aza:

1. 1-April-2013 – 7-April-2013, dose delay=no, dose change=no, planned dose=75mg/m2, actual dose=75mg/m2

2. 29-April-2013 – 5-May-2013, dose delay=yes, dose change=no, planned dose=75mg/m2, actual dose=0mg/m2

3. 6-May-2013 – 12-May-2013, dose delay=no, dose change=no, planned dose=75mg/m2, actual dose=75mg/m2

b. For Pan:

1. 3-April-2013 – 15-April-2013, dose delay=no, dose change=no, planned dose=30mg, actual dose=30mg

2. 29-April-2013 – 7-May-2013, dose delay=yes, dose change=no, planned dose=30mg, actual dose=0mg

3. 8-May-2013 – 20-May-2013, dose delay=no, dose change=no, planned dose=30mg, actual dose=30mg

- Situation 2: Dose interruption:

If one or more administrations have been skipped in one cycle, they must be considered as Dose Delays (there is no option for Interruption in the CRF).

Example: 5-Aza Cycle starts on 20-Jan-13, dose not administered on 23-Jan and 24-Jan, cycle ends on 26-Jan-13). Three records are needed:

1) enter the actual dose received, the true start date and the date of the last administration before the interruption (e.g. 20-Jan-2013 – 22-Jan-2013)

2) enter actual dose = 0 mg, select dose Change = No and Dose delay = Yes, and the start and end date of the interruption (e.g. 23-Jan-2013 – 24-Jan-2013)

3) enter the actual dose received, the date of the restart of the treatment and the true end date (e.g. 25-Jan-2013 – 26-Jan-2013)