DOCUMENT: Statistical Analysis Plan

PROTOCOL: MEI-011

A Two-Stage, Open-Label Phase 2 Study of Pracinostat and Azacitidine in Patients with IPSS-R High and Very High Risk Myelodysplastic Syndromes Previously Untreated with Hypomethylating Agents

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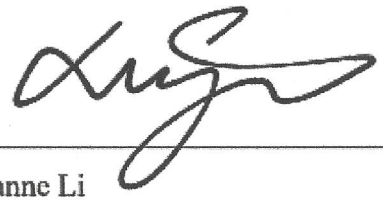
SPONSOR: MEI Pharma, Inc. on behalf of Helsinn Healthcare

PREPARED BY: Clinipace Worldwide

AUTHOR: Barbara Collins, BSc PhD
Senior Biostatistician, US Biostatistics
Clinipace Worldwide

APPROVAL SIGNATURES

SIGNATURE: DATE:



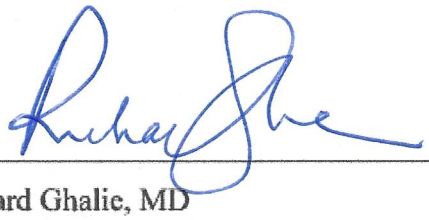
8/28/20

Joanne Li
Senior Director, Biometrics
MEI Pharma, Inc.

Signed by: Barbara Collins
Senior Statistician
Reason: I am the author of this document
Date & Time: Aug 28 2020 1:17 PM

DocuSign

Barbara Collins, BSc PhD
Senior Biostatistician
Clinipace Worldwide



29 AUG 2020

Richard Ghalie, MD
Senior Vice President, Clinical Development
MEI Pharma, Inc.

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ABBREVIATIONS

AE	Adverse event
CFB	Change from baseline
CR	Complete response/remission
CRi	Complete remission with incomplete blood count recovery
CRF	Case Report Form
CTCAE	Common Toxicity Criteria for Adverse Events
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event free survival
HI	Hematologic improvement
IPSS-R	Revised International Prognostic Scoring System
IWG	International Working Group
KM	Kaplan-Meier
MDS	Myelodysplastic Syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
ORR	Overall response rate
OS	Overall survival
PD	Progressive Disease
PFS	Progression Free Survival
PK	Pharmacokinetic
PP	Per Protocol
PR	Partial remission
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCT	Stem Cell Transplant
SD	Stable disease
STD	Standard deviation
TE	Treatment Emergent
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
WHO	World Health Organization

1 INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of clinical protocol MEI-011. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and electronic case report forms (eCRFs) for details of study conduct and data collection. Pharmacokinetic analyses and reporting are not included in this analysis plan.

2 STUDY OBJECTIVE(S), TREATMENTS, AND ENDPOINT(S)

2.1 Study Objectives

The purpose of this Phase 2 study is to evaluate the safety, tolerability, and efficacy of pracinostat and azacitidine as a combination treatment for subjects with Revised International Prognostic Scoring System (IPSS-R) high and very-high risk myelodysplastic syndromes (MDS) [3].

2.1.1 Primary Objectives

The primary objectives of this study are:

- To define the safety and tolerability of pracinostat plus azacitidine in high/very high risk MDS
- To define the rate of overall response rate (ORR), defined as complete remission (CR) and partial remission (PR), of pracinostat plus azacitidine in high/very high risk MDS

2.1.2 Secondary Objectives

The secondary objectives of this study are:

- Complete response (CR) rate
- Overall hematologic improvement (HI) response rate
- Clinical benefit rate, defined as rate of CR + PR + HI + Marrow CR
- Rate of cytogenetic complete response/remission
- Duration of response (DoR)
- Rate of leukemic transformation
- Duration of event-free survival (EFS)
- Duration of progression-free survival (PFS)
- Duration of overall survival (OS)

2.2 Treatment Groups

All Stage 1 and Stage 1b subjects will receive pracinostat and azacitidine. Treatment will be open-label.

2.3 Study Endpoints and Evaluations

2.3.1 Primary Endpoints

The primary efficacy endpoint is overall response rate (ORR) – defined as the proportion of subjects with confirmed complete response (CR) or partial response (PR) according to IWG criteria [1]. The ORRs will be assessed for both stages.

The primary safety endpoint is subject incidence of treatment emergent adverse event (TEAEs).

2.3.2 Secondary Endpoints

The secondary efficacy endpoints are:

- Complete remission (CR) rate: proportion of subjects with confirmed CR (i.e. 2 CRs at least 28 days apart) per IWG criteria. CR is defined as:
    - Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines; persistent dysplasia will be noted.
    - Peripheral blood (in the absence of transfusions)
        - Hemoglobin ≥ 11 g/dL
        - Platelets ≥ 100×10^9/L
        - Neutrophils ≥ 1.0×10^9/L
        - Blasts 0%
- Overall hematologic improvement (HI) rate: proportion of subjects who demonstrate major hematologic improvement per IWG criteria, for at least one criterion. Only subjects with pre-treatment abnormal values will be considered for this evaluation at 8 weeks.
- Clinical benefit rate (CBR): proportion of subjects with confirmed CR, PR, Marrow CR, or HI. All subjects who achieve hematologic CR, PR, marrow CR (with or without HI), or HI without marrow CR per IWG will be considered responders. PR is defined as all of the CR criteria if abnormal before treatment except bone marrow blasts, which can be decreased by ≥ 50% over pretreatment but still > 5%, and cellularity and morphology are not relevant. Marrow CR is defined, only in patients with MDS with excess blasts, as:
    - Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment
    - Peripheral blood: if HI responses, they will be noted in addition to marrow CR
- Relapse: after CR or PR, at least one of:
    - Return to pretreatment bone marrow blast percentage

  - Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets
  - Reduction in hemoglobin concentration by ≥ 1.5 g/dL or transfusion dependence
- Cytogenetic complete response/remission rate: proportion of subjects with disappearance of the chromosomal abnormality without appearance of new ones, by cytogenetic assessment in the subset of subjects with abnormal cytogenetics at baseline.
- Duration of response (DOR) will be derived in 2 ways: for subjects who achieve CR or PR (primary), and for subjects who achieve CR, PR, marrow CR or HI: time from initial determination of response to time of disease progression or death on study, whichever occurs first. For subjects who are alive and have not experienced disease progression on study (prior to receiving subsequent/new treatment or stem cell transplant), duration of response will be censored at the day of last disease assessment.
- Leukemic transformation rate: leukemic transformation at landmark time points of 6, 12, 18, and 24 months.
- Event-free survival (EFS), defined as the time from the first day of study drug administration (Day 1) to disease progression, relapse or death from any cause. Subjects who are alive and free from disease progression will be censored at the date of last disease assessment .
- Progression-free survival (PFS): time from the first day of study drug administration (day 1) to progression per IWG criteria, or death on study. Subjects who are alive and free from disease progression will be censored at the date of last disease assessment.
- Overall survival (OS): time from the first day of study drug administration (day 1) to death from any cause on study. Subjects who are alive will be censored at the date of last visit or contact with the investigator.
- Time to Stem Cell Transplant (SCT): time from the first day of study drug administration (day 1) to SCT, for subjects with SCT. If no SCT date can be confirmed, SCT date will be imputed as study drug discontinuation day.

For each of DOR, EFS, PFS and OS, in the sensitivity analyses, subjects with no events who stopped treatment and received SCT will be censored at the SCT day (either confirmed SCT day, or study drug treatment discontinuation day, if no SCT date can be confirmed) even if there were events which occurred after the SCT date.

- For both stages, the rate of treatment discontinuation in the first 3 cycles of therapy due to possibly safety-related reasons will be used as a secondary endpoint to evaluate the safety and tolerability. Progressive disease and transplant are reasons to discontinuation related to efficacy, therefore these events will be excluded from the analysis. All the other reasons for treatment discontinuation will be considered as possibly safety-related, therefore will be included in the analysis as events.

3 STUDY DESIGN

3.1 Overall Study Design

This study is a two stage Phase 2 trial in subjects with IPSS-R high and very high risk myelodysplastic syndromes (MDS) previously untreated with hypomethylating agents.

Stage 1 is an open-label portion in approximately 40 evaluable subjects will be treated with pracinostat and azacitidine. The goal of Stage 1 is to evaluate treatment tolerability – based on whether the combination regimen of pracinostat and azacitidine's rate of treatment discontinuation due to possibly safety reasons in the first 3 cycles of therapy is not significantly higher than 10%, and to determine if the observed efficacy justifies expansion of enrollment in Stage 1b based on ORR.

Stage 1b is an open-label expansion to achieve a total enrollment of approximately 60 subjects evaluable for efficacy, inclusive of Stage 1 and Stage 1b enrollment.

4 SAMPLE SIZE CONSIDERATIONS

Approximately 60 subjects evaluable for efficacy will be enrolled: approximately 40 in Stage 1 and 20 in Stage 1b. Non-evaluable subjects will be replaced.

4.1 Sample Size Determination for Stage 1

The goal of Stage 1 is to establish if this pracinostat + azacitidine regimen is safe and tolerable, as measured by the rate of treatment discontinuation due to possibly safety related reasons in the first 3 cycles of therapy. An discontinuation rate of 10%, based on that was observed in the azacitidine + placebo group in Study MEI-003 will be used as the threshold for safety evaluation. The 95% CI approach is utilized to estimate the sample size in Stage 1. A rate of treatment discontinuation of 22.5%, the midpoint between the discontinuation rates in the azacitidine + placebo (10%) and azacitidine + pracinostat (32%) groups, respectively, in Study MEI-003, is assumed to be the estimated discontinuation rate due to possibly safety related reasons.

With a sample size of 40 subjects, the study will be stopped if ≥ 9 subjects (22.5%, 95% CI: 10.8–38.4%) discontinue in the first 3 cycles. Under this scenario, the lower bound of the 95% CI is > 10 % (above the pre-specified desired goal).

In addition to the discontinuation threshold, the lower bound of 95% CI for an observed ORR of ≥ 25% will be desired to support opening Stage 1b of the study because it is expected that azacitidine alone results in an ORR of approximately 25% in high/very high-risk MDS. For example, with a sample sizeof N=40 and an assumed ORR of 45% for the azacitidine + pracinostat combination regimen, the 95% CI using exact method is (29.3%, 61.5%) with the lower bound higher than 20%.

4.2 Total Sample Size Determination

This study is intended to provide preliminary efficacy information to serve as a basis for a subsequent confirmatory study. Published studies have reported an ORR of approximately 25% (range 20-32%) with azacitidine alone at higher risk of MDS ([2], [4], [5]). An ORR of 40% with pracinostat plus azacitidine will be considered as clinically meaningful improvement compared to azacitidine alone. With a sample of

60 subjects, the lower bound of the 95% CI of an observed ORR of 40% is 27.6%, higher than the expected ORR with azacitidine alone, and will support continued evaluation of pracinostat plus azacitidine in a larger study in high risk MDS. The table below lists the lower bound of the 95% CI for a range of ORR and indicates that a sample of 60 subjects is informative for future development and shows that doubling the sample size to 120 subjects will only increase the precision of the 95% CI by approximately 4%.

	Lower Bound 95% CI of ORR	
ORR	N=60	N=120
50%	36.8	40.7
45%	32.1	35.9
40%	27.6	31.2
35%	23.1	26.5
30%	18.8	22.0

5 ANALYSIS POPULATIONS

5.1 Safety Population

The Safety Population is defined as all subjects who have been treated. The Safety population will be used for safety analyses.

5.2 Intent to Treat (ITT) Population

The Intent to Treat (ITT) population is defined as all enrolled subjects and is identical to the Safety Population. In this open-label single arm study, subjects who received at least one dose of study drug are defined as enrolled. The ITT population will be used for efficacy analyses.

5.3 Efficacy Evaluable (EE) Population

The Efficacy Evaluable (EE) population for endpoints requiring both bone marrow and peripheral blood assessments is defined as all subjects who

- received at least 2 cycles of therapy and a follow-up bone marrow AND peripheral blood assessments
- or experienced PD prior to completion of 2 cycles of therapy.

The Efficacy Evaluable (EE) population for endpoints requiring either bone marrow or peripheral blood assessment is defined as all subjects who

- received at least 2 cycles of therapy and a follow-up bone marrow OR peripheral blood assessments depending on the corresponding endpoints

or experienced PD prior to completion of 2 cycles of therapy.

The EE population will be used for key efficacy analyses as supportive analyses.

5.3 Per Protocol (PP) Population

The Per Protocol (PP) population is defined as all treated subjects without major protocol deviations, as detailed in section 8.3. The PP population will be used for the primary efficacy analysis.

6 CONSIDERATIONS FOR DATA ANALYSIS

6.1 Programming Environment

All analyses will be conducted using SAS® version 9.3 or above.

6.2 Strata and Covariates

There are no planned strata or covariate-adjusted analyses.

6.3 Subgroups

The following analyses will be broken down overall as well as by risk factor (high vs. very high risk group by IPSS-R), baseline characteristics (Age: <65 vs 65+, Gender, Bone marrow blasts <5% vs ≥5%) , primary vs. secondary MDS (secondary MDS is defined as MDS in patients treated with chemo or radiation for a prior malignancy), and undergoing transplant (yes vs no):

Overall Response
Clinical Benefit
Event Free Survival
Overall Survival

6.4 Multiple Comparisons and Multiplicity

There are no planned adjustments for multiple hypothesis testing.

6.5 Significance Level

No formal hypothesis testing is planned.

6.6 Statistical Notation and Methodology

Unless stated otherwise, the term "descriptive statistics" refers to the number of subjects (n), mean, median, standard deviation (SD), minimum (min), and maximum (max) for continuous data and frequencies (counts and percentages) for categorical data. Min and max values will be rounded to the precision of the original value, means and medians will be rounded to 1 decimal place greater than the precision of the original value, and STDs will be rounded to 2 decimal places greater than the precision of the original value. Percentages will be rounded to the nearest whole number (zeros will not be displayed), with values of "<1%" and ">99%" shown as necessary for percentages falling near the boundaries. P-values will be presented with 3 decimal places of precision, and values less than 0.001 will be presented as "<0.001".

Unless otherwise noted, all data collected during the study will be included in subject data listings and will be sorted by dose cohort, subject number, and date/time within each subject.

7 DATA HANDLING METHODS

7.1 Visit Windows

Day 1 will be the date corresponding to the first administration of study drug.

The screening assessments and the treatment/post-treatment assessments will be partitioned into the following two visit windows:

- A screening window, beginning on Day -14 and ending on Day -1.
- A treatment window, beginning on Day 1 and ending on the Study Day corresponding with the End of Study (EOS) visit.

Subject visits will be presented according to the nominal visit as obtained upon the eCRF. All values will be included in the subject data listings.

7.2 Date Values

The missing component(s) of incomplete dates (e.g. start and/or stop dates of AE, concomitant medication, medical history) will be assumed as the most conservative value possible. For example, if the start date has a missing day value, the first day of the month will be imputed for study day computations, etc. If day is missing for an end date, the last day of the month will be imputed. If the start date has a missing month value, the first month of the year will be imputed for study day computations, etc. If month is missing for an end date, the last month of the year will be imputed. For determination of treatment-emergent status, the start date will be imputed as the date of the first dose of study drug.

Date imputation will only be used for computational purposes such as treatment-emergent status, etc. Actual data values, as they appear in the original eCRFs, will be presented in the subject data listings.

7.3 Other Missing Values

Every effort will be made to obtain required data at each scheduled evaluation from all subjects who have been enrolled. There will be no imputation for missing data.

7.4 Data Derivations

Baseline values will be considered as the last non-missing assessment prior to the first administration of either study drug (pracinostat or azacitidine). Assessments performed prior to Day 1 for all other study procedures will be assumed to have been performed prior to administration of either study drug. Unless otherwise specified, change from baseline (CFB) calculations for a treatment window assessment will be the applicable treatment window assessment minus the baseline assessment (i.e., CFB = treatment window assessment – baseline). If either the treatment window assessment value or the baseline value is/are missing, then CFB will be set to missing.

For a given date within the screening window, Study Day will be computed as the given date minus Day 1 (i.e., Study Day = Date – Day 1).

For a given date within the treatment window, Study Day will be computed as the given date minus Day 1 plus 1 (i.e., Study Day = Date – Day 1 + 1).

Age will be calculated from the date of birth to the date of informed consent.

The following will define prior medication use versus concomitant medication use:

- Prior: Medication use ended before Day 1;
- Concomitant: Medication use (initiation date, or the stop date) is on or after Day 1.

8 STUDY POPULATION

Unless otherwise stated, all study population analyses will be performed using the ITT Population (see Section 5.2). Subjects who are approved by the Medical Monitor, but never dosed are not included in listings such as "Demographics" and instead only included in a table of Screen Failures or Subjects excluded from analysis populations. Unless otherwise stated, summaries will be summarized in a total group.

8.1 Subject Enrollment

Subject enrollment will be summarized as the number and percentage for each analysis population overall. Subjects who were never dosed will not be included in "enrolled". The denominators for calculating percentages will be based on the number of enrolled subjects.

A summary of the number of subjects who were screen failures along with the reasons for screen failure will be provided overall. The number of subjects enrolled but never treated will be provided for the total group.

Enrollment information will be provided in a data listing by subject.

8.2 Subject Disposition

Subject disposition will be presented for the ITT population using descriptive statistics. The number and percentage of subjects who receive at least one dose of study drug (pracinostat or azacitidine), subjects who have completed the study versus discontinued from the study, and subjects who discontinued from the study with their accompanying reason for discontinuation summarized for the total group. The denominators for calculating percentages will be based on the number of subjects for the total group.

Subjects who discontinued prior to dosing will be excluded from the analysis and treated as a screen failure. Discontinued subjects will be provided in a data listing by subject.

8.3 Protocol Deviations

Major protocol deviations are defined to be those deviations that could potentially bias either efficacy or safety summaries of the study. Subjects associated with major protocol deviations will be identified and documented prior to database lock.

Major deviations from the clinical protocol may include, but are not limited to:

- Informed consent issue
- Inclusion/exclusion criteria "other than those pre-planned via a waiver"
- Protocol required evaluation not completed
- Non-compliance with study drug administration
- Received excluded treatment or prohibited medication
- Developed withdrawal criteria but not withdrawn

The number and percentage of subjects with major deviations and the number of deviations will be summarized by type of deviation and overall. Summaries will be provided for the total group. The denominators for calculating percentages will be based on the number of subjects in the ITT population for the total group.

All protocol deviations not classified as major protocol deviations will be classified as minor protocol deviations.

All protocol deviations will be provided in a data listing by subject.

8.4 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria deviations will be provided in a data listing by subject.

8.5 Demographic and Baseline Characteristics

Subject demographics at screening include gender; age; race and ethnicity; height; weight; BMI; and baseline disease severity (IPSS-R and IPSS overall score and sub-components), and ECOG Performance Status, MDS WHO classification [3].

Gender, ethnicity, race, and disease history will be summarized as the number and percentage (n, %) of subjects within each category for the total group. Denominators used in the calculation of percentages will be based on the number of subjects in the ITT population for the total group.

Age, weight, height and BMI will each be summarized as a continuous variable using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for the total group.

Demographic characteristics will be provided in a data listing by subject.

8.6 Prior Therapies

8.6.1 Prior and Concomitant Transfusion Therapy

Prior and concomitant transfusion therapies will be summarized by product (fresh frozen plasma, packed RBCs, platelets, whole blood, plasma, other) and volume used for the total group.

Transfusion therapies will be reported in a data listing by subject.

8.6.2 Prior and Concomitant Stem Cell Transplant Therapy

Prior and concomitant stem cell transplant therapies will be summarized by type (autologous, allogenic, syngeneic, unknown, other) and units provided for the total group.

Stem cell transplants will be reported in a data listing by subject, including age, diagnosis, IPSS-R and IPSS score, best response obtained and number of cycles received for each transplanted subject.

8.6.3 Prior MDS Therapy

Prior MDS therapy will be summarized by therapy class and coded termfor the total group.

Prior MDS therapy will be reported in a data listing by subject.

8.7 Medical History

Medical history (including smoking history but excluding prior MDS therapies) will be summarized for each medical history code with descriptive statistics for the total group. Denominators for calculating percentages will be based on the number of subjects in the analysis population for each dose cohort and overall.

A summary table of smoking assessment will be summarized with descriptive statistics for the total group. Under protocol amendment 2, smoking assessment was added at days 1, 15 and 22 of each cycle

and the end of treatment visit. Records recorded as "Not Done", as the visit was prior to this addition, will not be included in the summary table.

A comprehensive data listing of medical history by subject will also be provided.

9 EFFICACY ANALYSIS

The ITT population will be used for summaries and analyses of efficacy described below unless otherwise stated. In addition, the primary efficacy will also be produced for the EE and PP populations. If the PP and ITT populations are identical, the PP tables will not be provided.

In this study, efficacy will be assessed by response to treatment with pracinostat and azacitidine. Response to treatment will be determined using the IWG criteria for MDS.

A summary of disease response will be provided using frequencies (counts and percentages). Denominators for calculating percentages will be based on the number of subjects in the ITT population.

Response to treatment will be provided in a data listing by subject.

9.1 Primary Endpoint Analysis

Overall response rate
The primary efficacy endpoint is overall response rate (ORR) defined as complete remission (CR) or partial remission (PR) per IWG criteria. The ORR and associated 95% confidence interval will be calculated using an exact binomial distribution approach for each of the ITT, EE and PP populations. For the PP population, the response rate will also be summarized by treatment schedule. In addition, a waterfall plot of the percentage change in blasts will be provided, and a forest plot of the ORR and corresponding 95% confidence intervals will be provided for each of the risk factors detailed in section 6.3.

If the ORR is shown to differ between the two treatment schedules, additional tables split by treatment schedule may be provided,

9.2 Secondary Endpoint Analysis

Rate of Discontinuation due to possibly safety reasons
For both stages, the rate of treatment discontinuation in the first 3 cycles of therapy due to possibly safety-related reasons will be used as a secondary endpoint to evaluate the safety and tolerability. The rate of subject discontinuation in the first 3 cycles and associated 95% confidence interval will be calculated using an exact binomial distribution approach.

Progressive disease and transplant are reasons to discontinuation related to efficacy, therefore these events will be excluded from the analysis. All the other reasons for treatment discontinuation will be considered as possibly safety-related, therefore will be included in the analysis as events.

9.2.1 Clinical Response

Clinical response rates will be based on the best response achieved by each patient in the following hierarchy:

CR -> PR -> Marrow CR -> SD -> PD

The response rate is based on confirmed response, the following rules will be taken into account:

If a patient has 2 CRs at least 28 days apart, best response is CR;

If a patient has at least 1 PR followed by 1 CR at least 28 days later, but no subsequent CR (ie the CR is not confirmed), best response is PR;

If a patient has 2 PRs at least 28 days apart, but no subsequent CRs, best response is PR;

If a patient has at least 1 Marrow CR followed by 1 CR or PR at least 28 days later, but no subsequent CR or PR (ie the CR/PR is not confirmed), best response is Marrow CR;

If a patient has 2 Marrow CRs at least 28 days apart, but no subsequent CRs or PR, best response is Marrow CR;

If a patient has 2 stable disease (SD) at least 28 days apart, but no subsequent PD, best response is SD.

9.2.1.1 Complete Response (CR) rate

Complete Response (CR) rate will be defined as the proportion of subjects with confirmed CR (i.e. 2 CRs at least 28 days apart) according to IWG criteria, as defined in section 2.3.2. Subjects achieving IWG criteria on bone marrow (≤ 5% myeloblasts with normal maturation of all cell lines), achieving IWG criteria on Peripheral blood at next 6 cycles, and confirmed achieving IWG criteria on Peripheral blood again with at least 28 days apart will be defined as achieving CR.

Subjects who are not evaluable for response for any reason will be considered as not achieving CR. The response rate and associated 95% confidence interval will be calculated using an exact binomial distribution approach for the ITT, EE and PP populations.

9.2.1.2 Overall hematologic improvement (HI) response rate

Overall hematologic improvement (HI) response rate will be defined as the proportion of subjects who demonstrate confirmed major hematologic improvement as defined by IWG criteria (i.e. 2 HIs at least 8 weeks apart), for at least one criterion. Only subjects with pre-treatment abnormal values will be considered for this endpoint. The response rate and associated 95%. confidence interval will be calculated using an exact binomial distribution approach for the ITT, EE and PP populations.

9.2.1.3 Clinical Benefit rate (CBR)

Clinical benefit rate (CBR) will be defined as the proportion of subjects with confirmed CR, PR, marrow CR, or HI. All patients who achieve hematologic CR, PR, marrow CR (with or without HI), or HI without marrow CR per modified IWG response criteria will be considered responders. The response rate and associated 95%. confidence interval will be calculated using an exact binomial distribution approach for the ITT, EE and PP populations. In addition, a forest plot of the ORR and corresponding 95% confidence intervals will be provided for each of the risk factors detailed in section 6.3.

9.2.1.4 Cytogenetic Complete Response/Remission rate

Cytogenetic complete response/remission rate will be defined as the proportion of subjects with disappearance of the chromosomal abnormality without appearance of new ones, by cytogenetic assessment in the subset of subjects with abnormal cytogenetics at baseline. The response rate and associated 95%. confidence interval will be calculated using an exact binomial distribution approach.

9.2.1.5 Leukemic Transformation rate

Leukemic transformation rate will be determined at landmark time-points of 6, 12, 18, and 24 months and present the transformation rate and corresponding 95% confidence interval.

9.2.2 Time-to-Event Endpoints

9.2.2.1 Duration of Response (DOR)

Duration of Response (DOR) will be analysed for the patients who achieved CR or PR, and for patients who achieved CR, PR, marrow CR or HI separately, and present the median time and associated 95%

confidence interval, analyzed by the Kaplan-Meier method. In addition Kaplan-Meier plots will be provided. Data will be censored as detailed in section 2.3.2.A sensitivity analysis will be performed censoring at the confirmed SCT day, or study drug treatment discontinuation day, if no SCT date can be confirmed. This will be analysed for the ITT population, and will present the median time and associated 95% confidence interval, analyzed by the Kaplan-Meier method. In addition, a Kaplan-Meier plot will be provided. These will be repeated for each of the risk factors detailed in section 6.3.

9.2.2.2 Event Free Survival (EFS)

Event Free Survival (EFS) will be analysed for the EE population and present the median time and associated 95% confidence interval, analyzed by the Kaplan-Meier method. In addition a Kaplan-Meier plot will be provided. These will be repeated for each of the risk factors detailed in section 6.3. Data will be censored as detailed in section 2.3.2.

A sensitivity analysis will be performed censoring at the confirmed SCT day, or study drug treatment discontinuation day, if no SCT date can be confirmed. This will be analysed for the ITT population, and will present the median time and associated 95% confidence interval, analyzed by the Kaplan-Meier method. In addition, a Kaplan-Meier plot will be provided. These will be repeated for each of the risk factors detailed in section 6.3.

9.2.2.3 Progression-Free Survival (PFS)

Progression-Free Survival (PFS) will be analysed for the EE population and will present the median time and associated 95% confidence interval, analyzed by the Kaplan-Meier method. In addition a Kaplan-Meier plot will be provided. Data will be censored as detailed in section 2.3.2.

A sensitivity analysis will be performed censoring at the confirmed SCT day, or study drug treatment discontinuation day, if no SCT date can be confirmed. This will be analysed for the ITT population, and will present the median time and associated 95% confidence interval, analyzed by the Kaplan-Meier method. In addition, a Kaplan-Meier plot will be provided. These will be repeated for each of the risk factors detailed in section 6.3.

9.2.2.4 Overall Survival (OS)

Overall Survival (OS) will be analysed for the ITT population, and will present the median time and associated 95% confidence interval, analyzed by the Kaplan-Meier method. In addition a Kaplan-Meier plot will be provided. These will be repeated for each of the risk factors detailed in section 6.3. Data will be censored as detailed in section 2.3.2.

A sensitivity analysis will be performed censoring at the confirmed SCT day, or study drug treatment discontinuation day, if no SCT date can be confirmed. This will be analysed for the ITT population, and will present the median time and associated 95% confidence interval, analyzed by the Kaplan-Meier method. In addition, a Kaplan-Meier plot will be provided. These will be repeated for each of the risk factors detailed in section 6.3.

10 SAFETY ANALYSIS

Unless stated otherwise, all safety analyses will be performed on the Safety Population.

10.1 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be set up for the study; details are provided in the protocol and DMC charter.

10.1 Adverse Events

Treatment-emergent adverse events (TEAEs) will be considered as any event occurring after receiving the first dose of either study drug until 30 days after the last study drug administration.

Treatment emergent adverse events (TEAE) will be classified into a standardized terminology using the Medical Dictionary for Regulatory Activities (MedDRA, version as referenced in the Data Management Plan) System Organ Classifications (SOC) and Preferred Terms (PT), and severity classified according to CTCAE version 4.03. All summaries of the incidence of treatment-emergent adverse events will be provided using the Safety Population for the total group. Although a SOC or PT may be reported more than once for a subject, each subject will only be counted once in the incidence count for that SOC or PT. Summaries of the following types of TEAEs will be provided:

- Overall Summary of Treatment Emergent Adverse Events (TEAEs);
- Summary of TEAEs by MedDRA SOC, PT and Grade (1 or 2, 3 and above);
- Summary of TEAEs related to pracinostat by MedDRA SOC, PT and Grade (1 or 2, 3 and above);
- Summary of TEAEs related to azacitidine by MedDRA SOC, PT and Grade (1 or 2, 3 and above);
- Summary of TEAEs by PT (in descending order)
- Summary of TEAEs leading to discontinuation from the study drug by MedDRA PT, sorted alphabetically by SOC and PT.
- Summary of Treatment Emergent Serious Adverse Events (TESAEs) by MedDRA PT, sorted alphabetically by SOC and PT;
- Summary of TESAEs related to pracinostat by MedDRA SOC, PT and Grade (1 or 2, 3 and above);
- Summary of TESAEs related to azacitidine by MedDRA SOC, PT and Grade (1 or 2, 3 and above);
- Summary of TESAEs by PT (in descending order)
- Summary of TEAEs leading to study treatment interruption
- Summary of TEAEs leading to azacitidine dose reduction

These summaries will present the number and percentage of subjects reporting an adverse event for each classification level. The denominators for calculating the percentages will be based on the number of exposed subjects in the Safety Population (i.e., study drug was administered) in the total group.

All adverse events, serious adverse events and deaths, and adverse events leading to discontinuation from the study will also be provided in data listings by subject.

10.3 Extent of Exposure

The duration of exposure (days) to study drug (pracinostat or azacitidine) will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) in the total group. Duration of exposure will be calculated as the difference between the date of last administration of study drug and the date of first administration of study drug plus 1 day.

The actual dose taken will be determined from the total number of doses taken (dispensed – returned) and the amount of drug per dose. This will be summarized using descriptive statistics for the total group for pracinostat dosing, and by scheduled and overall for azacitidine dosing. The number of cycles will be summarized using descriptive statistics and also in 3-month categories.

Exposure data including date, time, and dose of study drug administration at study site visits, diary dispense/return dates, and study drug dose modifications will be provided in separate data listings by subject. Number (%) of subjects with dose reductions and dose interruptions for both pracinostat and azacitidine will be provided.

10.4 Compliance

Treatment compliance will be assessed for each study drug (pracinostat and azacitidine) at each visit for which study drug can be determined, by comparing the expected number of daily doses and total dose of drug taken with the actual number of daily doses and total dose provided for each. The expected number of daily doses taken will be calculated as the sum of the appropriate number of doses taken and number of doses missed entries from the eCRF. Compliance will be calculated by the formula:

$$\text{Percent Compliance (pracinostat)} = 100 * \frac{\text{Actual \# of daily doses taken}}{\text{Expected \# of daily doses taken}}.$$

$$\text{Percent Compliance (azacitidine)} = 100 * \frac{\text{Actual doses administered}}{\text{Expected total dose to be taken } (\frac{\text{dose}}{\text{day}} * \text{ days})}.$$

If the number of doses taken is missing on the eCRF, it will be calculated based on the number of capsules dispensed and returned from the eCRF drug accountability workflow as total number dispensed – total number returned. If the number of doses missed is missing on the eCRF, it will be calculated based on the number of Study Days that have elapsed between the respective visits corresponding to study drug dispense and return.

Treatment compliance will be calculated for each subject/cycle and over all cycle for the Safety Population. Compliance values that are less than 0% will be set to 0%. A summary of treatment compliance will be presented using descriptive statistics for the Safety Population.

Compliance data will be presented within a data listing by subject.

10.5 Prior and Concomitant Medications

Medication usage will be coded using the World Health Organization (WHO) Drug Dictionary. Medication use will be presented for the Safety Population by WHO Drug Anatomical/Therapeutic/Chemical (ATC) category and WHO Drug preferred name. Medication use summaries will be presented for prior medication use (prior to first administration of study drug) and concomitant medication use. Summaries will be provided for the total group. Medications with partial start and/or stop dates, which cannot be definitely categorized as prior or concomitant treatment medications will be considered concomitant.

All summaries will present the number and percentages of subjects using each medication for the total group. The denominators for percentages will be the number of subjects in the analysis population for the total group. A summary of the reason for taking medication will also be provided.

Prior and concomitant medications will be provided in a data listing by subject.

10.6 Laboratory Evaluations

Absolute and change from baseline values for continuous parameters (analytes) over chemistry and hematology tests will be summarized by analyte, assessment, for the total group using descriptive statistics (mean, median, SD, minimum, maximum, and number of subjects). In addition, shifts from baseline CTCAE toxicity grade to worst on-treatment CTCAE toxicity grade will be presented by panel (chemistry and hematology) and analyte for the total group.

Data listings for laboratory parameters will be presented by subject.

10.7 Vital Signs

Vital sign measurements (blood pressure [systolic and diastolic], heart rate, and temperature, as well as height and weight) and change from baseline measurements will be summarized using descriptive statistics (mean, median, SD, minimum, maximum, and number of subjects) for the total group, and will also be presented as box plots over time.

10.8 Pregnancy Test

Serum pregnancy testing is required within 7 days of first study treatment for females of childbearing potential, and urine pregnancy tests may be performed at other visits as deemed necessary. Results of pregnancy tests will be provided in a data listing by subject.

10.9 Electrocardiograms (ECG)

The electrocardiogram (ECG) parameter QTcF interval will be assessed. Descriptive statistics for ECG measurements and change from baseline will be presented by assessment for the total group, and will also be presented as box plots over time.The triplicate values at each timepoint for a patient will be averaged, and the average value will be used in the summaries and plots.

In addition, the number and proportion of patients obtaining maximum treatment-emergent absolute QTcF >450ms and ≤480ms, >480ms and ≤500ms, and >500ms will be presented, along with the number and proportion of patients obtaining a maximum treatment-emergent QTcF increase from baseline >30ms and ≤60ms, and >60ms.

10.10 Physical Examinations

Physical examination (PE) will be conducted and any findings assessed for clinical significance (CS). CS findings from the Screening PE will be recorded as Medical History; CS findings for all other PEs will be captured as AEs.

10.11 ECOG Performance Status

The ECOG performance status is a rating scale used to assess how a subject's is progressing and to assess how the disease affects the daily living abilities of the subject. The score values are 0-5, where 0 indicates "fully active, able to carry on all pre-disease performance without restriction" and 5 indicates subject death.

A summary of ECOG performance status will be provided by visit for the total group using frequencies (counts and percentages).

ECOG performance status will be provided in a data listing by subject.

10.12 Bone Marrow Assessment

Bone marrow assessments (aspiration or biopsy) will be collected at intervals and used to determine treatment response. Bone marrow aspirate/biopsy will be examined for a range of assessments.

A data listing of bone marrow assessments will be presented by subject.

11 OTHER ANALYSES

11.1 Correlative/Pharmacodynamics Analysis

No pharmacodynamics analyses are planned.

11.2 Interim Analysis

The data from Stage 1 will be assessed to determine if the discontinuation rate due to possibly safety related reasons and preliminary efficacy data support proceeding to Stage 1b, but no formal interim analysis will be conducted.

The primary study analysis will be performed approximately 12 months after the last subject is enrolled in the study. At the completion of the primary analysis, the Sponsor will decide whether to terminate the study or continue study drug dosing in ongoing subjects.

11.3 Pharmacokinetic Analysis

Not Applicable.

12 END OF STUDY ANALYSIS

The final analysis will be conducted after the last subject discontinues the study or study is terminated by sponsor decision, and the resulting clinical database has been cleaned, quality checked, and locked.

Study database lock and unblinding will follow the applicable Clinipace Worldwide (CPWW) Standard Operating Procedures (SOPs). In brief, the sponsor and CPWW will agree and sign off on the database lock and protocol deviations classifications. After those steps have been completed, both the sponsor and CPWW will agree and sign off on the study unblinding form. Once this form has been finalized, the study database export coordinator will transfer the true randomization assignments into CPWW's statistical analysis computing area.

13 CHANGES FROM PROTOCOLLED ANALYSIS

The protocol states that the definition of overall survival is time from the first day of study drug administration (day 1) to death from any cause on study. Subjects who are alive will be censored at the date of last disease evaluation. This has been changed to the standardly used definition of time from the first day of study drug administration (day 1) to death from any cause on study. Subjects who are alive will be censored at the date of last visit or contact with the investigator.

The per protocol population has been renamed as the efficacy evaluable population, and an additional population, named the per protocol population, has been included in order to perform a sensitivity analysis excluding patients with major deviations.

14 REFERENCES

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