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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Amendment 2:	**25 June 2018**

PROTOCOL SIGNATURE PAGE

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

MEI-011

Amendment 2: 25 June 2018

This protocol was subject to critical review and has been approved by the following persons:

David Ramies, MD
Medical Monitor
MEI Pharma, Inc.

28 Jun 2018
Date

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

29 June 2018
Date

INVESTIGATOR SIGNATURE PAGE

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MEI-011

Amendment 2: 25 June 2018

Investigator Agreement

I have read, understand, and agree to conduct the study in accordance with the current protocol, and will:

- Personally supervise the conduct of this study.
- Conduct the study in accordance with International Council on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) E6 and applicable regulatory requirements.
- Comply with the procedures for data recording and reporting as required by regulatory authorities and the Sponsor.
- Permit monitoring, auditing, and inspection of study records as required by ICH GCP.
- Retain essential clinical study documents as required by ICH GCP and the Sponsor.

Principal Investigator Signature Date

Principal Investigator Name (Print)

SYNOPSIS

TITLE

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

PROTOCOL NUMBER

MEI-011

PHASE

Phase 2

STUDY DURATION

The total duration of the study is planned to be approximately 36 months: 24 months for enrollment and 12 months for follow-up until the primary study analysis.

PATIENT POPULATION

Subjects with high and very high risk myelodysplastic syndromes (MDS) according to the Revised International Prognostic Scoring System (IPSS-R) (Greenberg 2012). CMML 1 and 2 subjects will also be included.

NUMBER OF SUBJECTS AND STUDY CENTERS

This multicenter study will be conducted at approximately 25 sites.

Approximately 60 efficacy evaluable subjects will be enrolled in an open-label design in 2 stages (inclusive of Stage 1 and Stage 1 expansion [Stage 1b]):

Stage 1: Approximately 40 subjects

Stage 1 expansion (Stage 1b): Approximately 20 additional subjects to achieve a total of approximately 60 efficacy evaluable subjects for the entire study

PRIMARY OBJECTIVES

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

SECONDARY OBJECTIVES

Evaluate the following endpoints in patients with high/very high-risk MDS administered pracinostat plus azacitidine:

- Complete response (CR) rate
- Overall hematologic improvement (HI) 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
- Event-free survival (EFS)
- Progression-free survival (PFS)
- Overall survival (OS)

BACKGROUND

Higher risk MDS (high and very high risk in the IPSS-R classification) is a serious medical condition, with a median survival of only 0.8 years in very high-risk disease and 1.6 years in high-risk disease (Greenberg 2012). The only curative therapy is allogeneic stem cell transplantation (SCT), however most patients with MDS are not candidates for SCT given their typically advanced age, comorbidities, and lack of a suitable donor. Standard therapy with hypomethylating agents (HMAs) in intermediate-2/high-risk MDS provides modest responses, though azacitidine has been shown to improve survival when compared to conventional care regimens (Fenaux 2009). Patients who do not respond to HMAs or progress after therapy with HMAs have a very poor outcome, with a median survival of less than one year (Prebet 2011). Approaches to improving the treatment effect of hypomethylating therapy are clearly indicated.

Abnormal epigenetic silencing of important regulatory genes has been described in cancer, including MDS and acute myeloid leukemia (AML). The reduction of acetylation status of histones is one mechanism for this silencing. Inhibitors of histone deacetylases (HDACs) have been extensively studied in both hematologic and solid tumors. Histone deacetylases are enzymes involved in the remodeling of chromatin, and therefore, have a key role in the epigenetic regulation of gene expression.

Pracinostat, a potent, oral, pan-HDAC inhibitor was shown to have modest single-agent activity in myeloid malignancies. Synergistic interactions have been observed with multiple cytotoxic and targeted anti-cancer therapeutics; notably, the combination index with azacitidine ranged from 0.44 to 0.55. The maximum tolerated dose of single-agent pracinostat based on chronic administration was established at 60 mg every other day, 3 days each week for 3 weeks, followed by 1 week of rest, in 28-day cycles.

STUDY RATIONALE

A pilot study of pracinostat (60 mg, 3 alternate days each week for 3 consecutive weeks) administered in combination with azacitidine (75 mg/m^2 intravenously [IV] daily × 7 days) in 28-day cycles conducted in 10 patients with advanced MDS showed an encouraging overall response rate and cytogenetic responses. Pracinostat dose was reduced or treatment interrupted as clinically indicated to improve tolerability and maintain patients on therapy (Abaza 2017).

In the subsequent placebo-controlled Phase 2 study (MEI-003) conducted in 102 patients with higher-risk MDS, pracinostat (60 mg, 3 alternate days each week for 3 weeks) in combination with azacitidine (75 mg/m^2 for 7 days) in 28-day cycles failed to increase the CR rate, PFS, and OS compared to azacitidine + placebo (Garcia-Manero 2017). In that study, 26% of subjects in the pracinostat group discontinued study drugs in the first 3 cycles of therapy (by approximately Day 84) for reasons other than progressive disease or stem cell transplant compared to 10% of patients randomized to the placebo group. The most common cause for early discontinuations in the pracinostat group was adverse events (AEs), primarily fatigue and myelosuppression. Furthermore, in the intermediate-2 risk group, 14/30 patients (47%) randomized to pracinostat discontinued the study due to AEs or withdrawal of consent at any time in the study compared to 4/33 patients (12%) randomized to placebo, whereas in the high-risk group the rate of discontinuation due to AEs or withdrawal of consent was similar in the pracinostat group (27%) and placebo group (22%). In a post-hoc analysis, the subset of subjects who received at least 4 cycles of pracinostat/azacitidine and began Cycle 5 had a trend for better PFS and OS (hazard ratio [HR] = 0.67) compared to the control group. This suggests the lack of efficacy in the intent-to-treat (ITT) population may be due to early discontinuations and insufficient exposure to pracinostat/azacitidine.

This study will evaluate a regimen consisting of a lower dose of pracinostat in combination with the standard dose of azacitidine to determine if the rate of early discontinuation can be reduced, thereby improving efficacy.

DOSE SELECTION

This study will investigate a pracinostat dose of 45 mg, 25% lower than the dose used in Study MEI-003. Pracinostat will be administered at 45 mg, 3 days each week (e.g., Monday, Wednesday, Friday) for 3 weeks, followed by 1 week of rest, with azacitidine at the standard dose of 75 mg/m^2 for 7 days of each 28-day cycle.

The rationale for selecting a pracinostat daily dose of 45 mg for this regimen include:

- The dose of 45 mg has been used in prior Phase 2 studies in MDS and AML as the step-down dose level for subjects who did not tolerate the starting dose of 60 mg.
- In prior studies in MDS and AML, approximately 50% of subjects who achieved an objective response and received pracinostat for more than one year had their dose reduced from 60 mg to 45 mg, indicating this dose is efficacious and well tolerated.
- A dose of 40 mg was shown to induce a 2-fold increase in histone 3 acetylation (acH3) in 17 subjects with solid tumors, a level comparable to that achieved with a dose ≥ 60 mg but significantly higher than achieved with a dose of 20 mg, suggesting that a dose of 45 mg may be sufficient for full pharmacodynamic effects.
- A dose of 45 mg results in plasma concentrations greater than HDAC C1 inhibitory constant (Ki) for approximately 24 hours, suggesting adequate HDAC inhibition at this dose.

STUDY DESIGN

This is a Phase 2, two-stage study of the safety and efficacy of pracinostat in combination with azacitidine in patients with IPSS-R high and very high-risk MDS who are previously untreated with HMAs. Enrollment in this study will be limited to high/very high-risk MDS because this group represents the highest unmet need, with median survival of less than 18 months. Recognizing that additional safety and efficacy of pracinostat plus azacitidine is desirable before evaluating the treatment regimen in a placebo-controlled environment, the protocol is being amended to become a 2-stage open-label study comprising Stage 1 and Stage 1 expansion (Stage 1b).

Stage 1 will be conducted as an open-label single arm in approximately 40 evaluable subjects to assess if this regimen with a lower pracinostat dose results in a discontinuation rate that meets a predefined threshold and the observed efficacy justifies expansion to Stage 1b.

A discontinuation rate of approximately ≤ 10% in Stage 1, a rate comparable to that observed with azacitidine alone in Study MEI-003, would support expansion to Stage 1b. Stage 1b will be conducted as an open-label, single-arm to achieve a total enrollment of approximately 60 efficacy evaluable subjects, inclusive of Stage 1 and Stage 1b enrollment.

Study drugs should be continued until disease progression or intolerable toxicity. It is important to note that the median time to achieving a response with azacitidine alone is 4 to 5 months. Furthermore, the median time to achieving a CR in study MEI-003 was 4 cycles. Therefore, early (< 6 months) discontinuation of study therapy for 'no response' should be avoided. The Medical Monitor should be contacted prior to discontinuing study drugs in a subject to discuss the rationale for discontinuation.

After discontinuing study drugs, subjects will be followed every 3 months (± 1month) until death or study termination to collect information on disease status (i.e., improvement of disease response or disease progression), start of non-protocol therapies (e.g., stem cell transplant or an MDS-directed therapy) and survival.

The primary study analysis will be performed approximately 12 months after the last subject is enrolled in the study. The study duration is anticipated to be approximately 36 months: 24 months for enrollment and 12 months of follow-up until the primary analysis. At the completion of the primary analysis, the Sponsor will decide whether to terminate the study or continue study drug dosing in ongoing subjects.

STUDY DRUGS, DOSES, AND MODES OF ADMINISTRATION

Pracinostat: 45 mg administered orally 3 days each week (e.g., Monday, Wednesday, Friday) for 3 consecutive weeks, followed by 1 week of rest, in 28-day cycles.

In later cycles (i.e., after Cycle 4), 45 mg pracinostat can be reduced to orally 3 days each week × 2 weeks (instead of 3 weeks) or dose interruption is allowed to manage toxicity such as fatigue, gastrointestinal toxicity, or myelosuppression.

Azacitidine: All subjects will receive a standard regimen of azacitidine at 75 mg/m^2 for 7 days of each 28-day cycle. Administration will occur by subcutaneous (SC) injection, or intravenous (IV) infusion if SC injections are not tolerated, on one of two schedules:

- Schedule 1 – daily therapy on Days 1 through 7
- Schedule 2 – 5-2-2 schedule in which subjects receive azacitidine for 5 consecutive days (Days 1 through 5) with rest on Days 6 and 7, and resume azacitidine dosing the first two days of the next week (Days 8 and 9) of each 28-day cycle.

Subjects may be treated on either azacitidine schedule, however the preference is to have subjects stay on the same schedule during their participation in the study.

Azacitidine should be given at approximately the same time each day.

In the presence of toxicity, azacitidine dose reduction in Cycle 2 and subsequent cycles will be performed according to the azacitidine product labeling recommendations or local standards of care.

SUBJECT POPULATION

Inclusion Criteria

To be eligible for study participation, subjects must meet the following inclusion criteria:

1. Female or male subjects ≥ 18 years-of-age.

2. Histologically or cytologically documented diagnosis of MDS according to the World Health Organization (WHO) classification (Vardiman 2009, Arber 2016; Appendix B) with < 20% bone marrow blasts by morphology and a peripheral white blood cell (WBC) count of < 20,000/µL
   - If WBC ≥ 20,000/µL, cytoreduction with hydroxyurea is permitted prior to enrollment.
   - CMML-1 and CMML-2 subtypes are eligible for study participation.

3. Classified as high or very high risk according to the Revised International Prognostic Scoring System (IPSS-R) risk category (Appendix C). CMML-1 and CMML-2 subtypes will be considered high-risk MDS and will not require IPSS-R scoring.

4. Bone marrow biopsy (BMBx) and/or aspirate within 28 days prior to planned first study treatment (Cycle 1 Day 1).

5. Clinical indication for treatment with azacitidine.

6. Previously untreated with HMAs (prior therapy with transfusions, hematopoietic growth factors, or immunosuppressive therapy is allowed).
   a. Subjects who require the start of an HMA (e.g., azacitidine) due to progressing MDS may receive up to 1 cycle of azacitidine within 30 days prior to planned first dose (Cycle 1 Day 1).

7. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

8. Adequate organ function as evidenced by:
   - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × the upper limit of normal (ULN).
   - Total bilirubin ≤ 1.5 × ULN or total bilirubin of ≤ 2 mg/dL, whichever is higher. Total bilirubin < 3 x ULN for patients with Gilbert-Meulengracht Syndrome.
   - Serum creatinine ≤ 1.5 x ULN, or creatinine clearance ≥ 40 mL/min according to institutional standards (actual body weight should be used to calculate creatinine clearance).
   - QTcF interval ≤ 450 msec using the mean of triplicate electrocardiograms (ECGs).

9. Female subjects of childbearing potential and male subjects with female partners of childbearing potential are required to use two forms of acceptable contraception, including one barrier method, during their participation in the study and for 30 days following last dose. Female subjects of childbearing potential must not be breastfeeding, or planning to breastfeed, and must have a negative pregnancy test ≤ 7 days before first study drug administration. Male subjects must also refrain from donating sperm during their participation in the study.

10. Voluntary written informed consent before performance of any study-related procedure not part of normal medical care.

11. Have the willingness and ability to understand the nature of this study and to comply with the study and follow-up procedures.

Exclusion Criteria

Exclude subjects from this study if they do not fulfill the inclusion criteria, or if any of the following criteria are observed:

1. Bone marrow blasts ≥ 20%, indicating a diagnosis of acute myeloid leukemia (AML).

2. Received any of the following within the specified time frame prior to administration of study medication:
   - Any investigational agent within 14 days or 5 half-lives prior to enrollment, whichever is longer.
   - Hydroxyurea within 48 hours prior to first day of study treatment.
   - Hematopoietic growth factors: erythropoietin, granulocyte colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), or thrombopoietin receptor agonists at least 7 days (14 days for Aranesp), prior to study enrollment.
   - Major surgery within 28 days prior to first study treatment.

3. Subjects who have not recovered from side effects of previous therapy.

4. Cardiopulmonary function criteria:
    - Current unstable arrhythmia requiring treatment.
    - History of symptomatic congestive heart failure (New York Heart Association [NYHA] Class III or IV).
    - History of myocardial infarction, pulmonary embolism or cerebrovascular accident within 6 months of enrollment.
    - Current unstable angina.

5. Prior treatment for MDS with the HDAC inhibitors Zolinza (vorinostat), Belenodaq (belinostat), Farydak (panobinostat), Istodax (romidepsin/depsipetide), or investigational agent with significant action as an HDAC inhibitor.

6. Clinical evidence of central nervous system involvement.

7. Subjects with gastrointestinal (GI) tract disease causing the inability to take oral medication, malabsorption syndrome, a requirement for IV alimentation, prior surgical procedures affecting absorption, uncontrolled inflammatory GI disease (e.g., Crohn's disease, ulcerative colitis).

8. Uncontrolled infection with human immunodeficiency virus (HIV) or chronic hepatitis B or C.

9. Life-threatening illness unrelated to cancer or any serious medical or psychiatric illness that could, in the Investigator's opinion, potentially interfere with participation in this study.

10. Presence of a malignant disease within the last 12 months, with the exception of adequately treated in-situ carcinomas, basal or squamous cell carcinoma, non-melanomatous skin cancer, or malignancies treated with curative intent and no evidence of active disease in prior 12 months and felt to be low risk for recurrence. Other malignancies may be considered after consultation with the Medical Monitor.

11. An unwillingness or inability (including breastfeeding women, prohibited concomitant medications, uncontrolled infections, psychological, familial, sociological, or geographical conditions) to comply with study and/or follow-up procedures as outlined in the protocol.

12. Known hypersensitivity to any components of pracinostat, azacitidine or mannitol.

13. Current smoking or vaporizing of tobacco or cannabis-related products (use of patches, chewing tobacco, or nicotine gum is permitted). Subjects who stopped smoking at least 8 days prior to first pracinostat dosing can be enrolled, provided they refrain from smoking during the whole study.

CRITERIA FOR EVALUATION

Safety

Safety will be assessed by AEs (graded according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.03), laboratory safety tests including complete blood count (CBC) and serum chemistry, physical examination, vital signs, ECOG performance status, and 12-lead ECG.

Efficacy

Efficacy will be evaluated by Investigator assessments based on hematological and cytogenetic examination of peripheral blood and bone marrow aspirates and biopsy, as well as transfusions administered, using the revised International Working Group (IWG) response criteria for MDS (Cheson 2006). If deemed necessary during the conduct of the study, central verification of efficacy assessments will be performed by independent reviewers.

CYTOGENETIC AND MOLECULAR TESTING

Classical cytogenetics shall be required on BMBx and aspiration at screening, and subsequent assessments as indicated. Cytogenetics are performed as standard of care to classify the subject's MDS in the corresponding IPSS-R risk category and to determine cytogenetic remission/response.

Fluorescence in situ hybridization (FISH) and molecular tests (e.g., polymerase chain reaction) may be conducted as per institutional standard of care but are not required. If performed, the results should be documented in the case report form (CRF).

STATISTICAL METHODOLOGY

Sample Size

Approximately 60 subjects evaluable for efficacy will be enrolled, including approximately 40 evaluable subjects in Stage 1 and the remaining subjects in Stage 1b. Non-evaluable subjects will be replaced.

Sample size calculation for Stage 1

The goal of Stage 1 is to establish a pracinostat/azacitidine regimen with a discontinuation rate of approximately up to 10% in the first 3 cycles of therapy, a rate comparable to that observed in the azacitidine/placebo group in study MEI-003. The 95% confidence interval (CI) approach is utilized to estimate the sample size in Stage 1. The number of subjects to be enrolled is calculated such that the lower bound of the 95% CI of the discontinuation rate will be no more than 12% below the point estimate of 22.5%, the mid-point between the discontinuation rates in the azacitidine/placebo (10%) and azacitidine/pracinostat (32%) groups, respectively, in study MEI-003.

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) and the upper bound of the 95% CI is > 32% (higher than the discontinuation rate in study MEI-003).

It is also possible to conclude that the desired threshold of a discontinuation rate of $\leq 10\%$ has been achieved with fewer than 40 subjects treated in Stage 1. For example, if 4 discontinuations are observed in the first 32 subjects, the lower and upper bounds of the 95% CI around the observed discontinuation rate of 12.5% (4 of 32) are 3.5% and 29.0%, lower than reported with azacitidine/placebo and azacitidine/pracinostat, respectively, in study MEI-003. This would justify expanding enrollment in Stage 1b of the study after only 32 subjects have been treated for ≥ 3 cycles.

The Independent Data Monitoring Committee (IDMC), in coordination with the Sponsor, will determine when to open Stage 1b enrollment.

Total sample size calculation

Approximately 60 subjects evaluable for efficacy will be enrolled in the study: approximately 40 in Stage 1 and 20 in Stage 1b. An ORR of 40% in subjects with high/very high-risk MDS treated with pracinostat plus azacitidine will be considered a clinically meaningful improvement compared to a historical ORR of 25% with azacitidine alone in this subject population. With a sample size of 60 subjects, the lower limit of the 95% CI of an observed ORR of 40% is 27.6%, higher than the ORR anticipated with azacitidine alone, and will support continued evaluation of this treatment regimen in a larger study.

Statistical Analysis

All analyses will be descriptive. Binomial variables will be presented as frequency and 95% CI. Continuous variables will be presented as median, mean, range, and 95% CI. Time-to-event endpoints will be analyzed by the method of Kaplan-Meier. Comparisons between subject subsets will be exploratory.

Primary and exploratory analyses will be performed as described in detail in the study Statistical Analysis Plan.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

The following abbreviations are used in this study protocol:

Abbreviation	Explanation
acH3	histone 3 acetylation
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AST	aspartate aminotransferase
BMBx	bone marrow biopsy
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CMML	chronic myelomonocytic leukemia
CO_2	carbon dioxide
CR	complete response/remission
CRi	complete response/remission with incomplete blood count recovery
CRF	case report form
DoR	duration of response
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EFS	event free survival
FDA	US Food and Drug Administration
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
GI	gastrointestinal
G-CSF	granulocyte colony stimulating factor
GM-CSF	granulocyte macrophage colony stimulation factor
HDAC	histone deacetylase
HI	hematological improvement
HI-E	hematologic improvement on the erythrocytic lineage
HIPAA	Health Insurance Portability and Accountability Act

Abbreviation	Explanation
HMA	hypomethylating agent
HR	hazard ratio
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council on Harmonisation
IDMC	Independent Data Monitoring Committee
IPSS	International Prognostic Scoring System
IPSS-R	International Prognostic Score System Revised
IRB	Institutional Review Board
ISF	investigator site file
ITT	intent-to-treat population
IV	intravenous(ly)
IWG	International Working Group
Ki	inhibitory constant
LDH	lactate dehydrogenase
MDS	myelodysplastic syndrome
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PHI	protected health information
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
QTcF	corrected QT interval using Fridericia's formula
SAE	serious adverse event
SC	subcutaneous(ly)
SCT	stem cell transplantation
SD	stable disease
SOP	standard operating procedure
SSF	site study file
ULN	upper limit of normal
US	United States

Abbreviation	Explanation
TEAE	treatment emergent adverse event
WBC	white blood cell
WHO	World Health Organization

1 INTRODUCTION

1.1 Background

Abnormal epigenetic silencing of important regulatory genes has been described in various cancers, including myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) (Jones 2007). The reduction of acetylation status of histones is one mechanism for this silencing. Histone deacetylases (HDACs) are enzymes involved in the remodeling of chromatin, and therefore, have a key role in the epigenetic regulation of gene expression. Inhibitors of HDACs have been extensively studied in both hematologic and solid tumors. Four HDAC inhibitors have been approved to date by the US Food and Drug Administration (FDA) for the treatment of T-cell lymphoma, peripheral T-cell lymphoma, and multiple myeloma.

1.2 Pracinostat

Pracinostat is a rationally-designed, potent, oral, pan-HDAC (including Class I, II, and IV isoforms) inhibitor with pharmacokinetic (PK) properties allowing every other day dosing. The half-maximal inhibitory concentration (IC_{50}), across a broad range of human cancers in in vitro cytotoxicity assays, ranged from 0.1 to 1.5 μM, with the lowest values noted in leukemia and lymphoma cell lines. Synergistic interactions have been observed with multiple cytotoxic and targeted anti-cancer therapeutics; notably the combination index with azacitidine ranged from 0.44 to 0.55.

1.3 Preclinical Pharmacology

Results from pharmacology studies showed that pracinostat inhibits predominantly Class I and II HDACs (inhibitory constant [Ki] = 16 to 240 nM). It effectively inhibits acetylation of histones and various other target proteins in a variety of human tumor cell lines at the same concentrations as it inhibits proliferation and promotes apoptosis (IC_{50} = 0.1 to 1.5 μM). Lymphomas and tumors of hematological origin show the highest sensitivity.

The antitumor activity of orally administered pracinostat has been demonstrated in several xenograft mouse models of solid and hematological malignancies including colorectal cancer, ovarian cancer, prostate cancer, AML, and B cell lymphoma. As observed in the in vitro cell studies, hematological malignancies are most sensitive to the anti-tumor effects of pracinostat.

1.4 Clinical Experience

Pracinostat has been evaluated, either as a single agent or in combination with hypomethylating agents (HMAs), in over 430 patients with solid tumors and hematologic malignancies in multiple Phase 1 and Phase 2 clinical studies. In the initial studies, pracinostat was administered as a single agent and was found to be generally well-tolerated at doses up to 60 mg given 3 days each week (e.g., Monday, Wednesday, Friday) for 3 weeks on an every-4-week schedule. The most common manageable side effects often associated with drugs of this class, including pracinostat, are fatigue, gastrointestinal (GI) effects (nausea, vomiting, diarrhea), and myelosuppression. Please see the Investigator's Brochure (IB) for further information on

clinical studies conducted to date, adverse events (AEs) associated with pracinostat, and efficacy results.

Single-agent pracinostat has demonstrated modest activity in patients with advanced hematologic disorders. In a Phase 1 dose escalation study in 44 patients with various hematologic malignancies, pracinostat was evaluated at doses ranging from 20 to 120 mg administered orally every other day 3 times a week for 3 consecutive weeks, in a 4-week cycle. The maximum tolerated dose (MTD) was declared as 120 mg; due to dose reduction after multiple cycles of treatment, the recommended Phase 2 dose was determined to be 100 mg (Abaza 2017). Of 25 patients with AML enrolled in the study, one achieved a complete response/remission (CR) lasting 206 days, one achieved a partial response (PR) lasting 362 days, and four achieved stable disease (SD) for > 2 cycles. Three of 14 patients with intermediate or high-risk MDS achieved SD for 72 to 134 days.

A Phase 2 clinical study of oral pracinostat (60 mg every other day for 3 weeks per month) showed activity in 22 heavily pre-treated subjects with intermediate or high-risk myelofibrosis. Eight (36%) subjects experienced clinical benefit, with 6 (27%) experiencing reductions in splenomegaly (median 3 cm, range 1–4 cm) (Quintás-Cardama 2012a).

Because synergistic epigenetic effects were shown between HDAC inhibitors and HMAs, all subsequent studies have evaluated pracinostat in combination with the HMAs azacitidine and decitabine in myeloid malignancies AML, MDS, and myelofibrosis. Information on the evaluation of pracinostat in combination with HMAs in MDS is summarized in Section 1.5.

An open-label Phase 2 study evaluated pracinostat plus azacitidine in 50 patients ≥ 65 years of age with previously untreated AML and unfit to receive intensive induction chemotherapy (Study MEI-004). Pracinostat was administered orally at 60 mg every other day, 3 days a week for 3 weeks of each 4-week cycle in combination with azacitidine 75 mg/m^2 for 7 days of each cycle (Garcia-Manero 2017). The median age was 75 years (range 66 – 84 years); the Eastern Cooperative Oncology Group (ECOG) performance status was 0 – 1 in 84% and 2 in 16%; 66% had de novo AML and 34% had secondary AML; and the median bone marrow blasts was 40% (range 20 – 89%). The median number of treatment cycles was 6.5 (range 1 – 24+). Non-hematologic AEs grade ≥ 3 reported in > 5% of patients were fatigue 34%; anorexia 10%, cellulitis, pneumonia, asthenia, and sepsis in 8%; and urinary tract infection, nausea, back pain, hypoxia, hyponatremia, and syncope in 6%. The 30-day and 60-day mortality rates were 2% and 10%. Complete response was achieved in 21 patients (42%) and a CR with incomplete blood recovery (CRi) in 2 (4%). With a median follow-up of 21 months, the median overall survival (OS) was 19.1 months (95% confidence interval [CI], 10.0 – 26.52), and the 1-year and 2-year OS were 62% and 45%, respectively. These results compare favorably to historical data with single agent azacitidine in comparable populations and serve as the basis for conducting a Phase 3 study in patients with untreated AML unfit to receive intensive induction chemotherapy.

1.5 Rationale for the Study

Higher risk MDS in the Revised International Prognostic Scoring System (IPSS-R) classification is a serious medical condition, with a median survival of only 0.8 years in very high-risk disease and 1.6 years in high-risk disease. The only curative therapy is allogeneic stem cell

transplantation (SCT), however the vast majority of patients with MDS are not candidates for SCT given their typically advanced age, comorbidities, and lack of a suitable donor. Standard therapy with HMAs in intermediate-2 or high-risk MDS provides modest responses, though azacitidine has been shown to improve survival when compared to conventional care regimens (Fenaux 2009). Patients who do not respond to HMAs or progress after a response to HMAs have a very poor outcome, with median survival of less than one year (Prebet 2011). Approaches to improving the treatment effect of hypomethylating therapy are clearly indicated.

A pilot Phase 2 clinical study of pracinostat in combination with azacitidine was conducted in 10 subjects with advanced MDS and showed a CR + CRi rate of 78% and a cytogenetic complete response/remission of 56% (Abaza 2017). In this study, pracinostat was administered at 60 mg, on 3 alternate days each week for 3 consecutive weeks in combination with azacitidine (75 mg/m^2 intravenously [IV] or subcutaneously [SC] daily × 7 days). Pracinostat dose was reduced or treatment interrupted as clinically indicated to improve tolerability and maintain patients on therapy.

These positive findings led to the conduct of a placebo-controlled Phase 2 study (MEI-003) in 102 subjects with higher-risk MDS administered pracinostat (60 mg, 3 alternate days each week for 3 weeks) or placebo in combination with azacitidine (75 mg/m^2 for 7 days) in 28-day cycles (Garcia-Manero 2017). The median age was 69 years (range 26–90 years), 67% of subjects had IPSS intermediate-2 risk MDS and 33% had high-risk MDS. The rate of CR by Cycle 6, the study's primary endpoint, was 18% (9/51) in the pracinostat group compared to 33% (17/51) in the placebo group (p = 0.07). The cytogenetic response rate in the pracinostat group was 42% (14/33) compared to 55% (17/31) in the placebo group (p = 0.14). Hematologic improvement was 35% (15/43) and 55% (24/44) in the pracinostat and placebo groups, respectively (p = 0.51). Median duration of response (DoR) was 12 months and 9 months in the pracinostat and placebo groups, respectively (hazard ratio [HR] = 0.64, 95% CI 0.23 – 1.79). With a median duration of follow-up of 15 months, the median OS in the pracinostat and placebo group was 16 and 19 months, respectively (HR = 1.21, 95% CI, 0.65 – 2.23). The median event-free survival (EFS) was 9 months in both groups (HR = 0.82, 95% CI 0.46 – 1.46) and the 1-year OS was 60% in both groups.

In that study, 26% of subjects in the pracinostat group discontinued study drugs in the first 3 cycles of therapy (by Day 84) for reasons other than progressive disease (PD) or SCT as compared to 10% of subjects randomized to the placebo group. The most common cause for early discontinuations in the pracinostat group was AEs; primarily fatigue and myelosuppression. Furthermore, in the intermediate-2 risk group, 14/30 subjects (47%) randomized to pracinostat discontinued the study due to AEs or withdrawal of consent at any time in the study compared to 4/33 subjects (12%) randomized to placebo, whereas in the high-risk group, the discontinuation rate due to adverse events/withdrawal was comparable in the 2 treatment arms; 27% in pracinostat versus 22% in placebo.

In a post-hoc analysis, the subset of subjects who received at least 4 cycles of pracinostat + azacitidine and began Cycle 5 had a trend for better progression-free survival (PFS) and OS (HR = 0.67) compared to the control group. This suggests the lack of efficacy in the intent-to-treat (ITT) population may be due to early discontinuations and insufficient exposure to pracinostat. This is further supported by the data from Study MEI-004 in elderly AML where

the discontinuation rate was lower (8% in the first 2 cycles) resulting in substantial treatment efficacy, with a CR rate of 42% and a median survival of 19.1 months (Garcia-Manero 2016). Therefore, this current study will evaluate a regimen consisting of a lower dose of pracinostat in combination with the standard dose of azacitidine to determine if the rate of early discontinuation can be reduced, thereby improving efficacy.

1.6 Rationale for Pracinostat Dose Selection

This study will investigate a pracinostat dose of 45 mg, 25% lower than the dose used in Study MEI-003. The rationale for selecting a pracinostat daily dose of 45 mg for this regimen include:

- The dose of 45 mg has been used in prior Phase 2 studies in MDS and AML as the step-down dose level for subjects who did not tolerate the starting dose of 60 mg.
- In prior studies in MDS and AML, approximately 50% of subjects who achieved an objective response and received pracinostat for more than one year had their daily dose reduced from 60 mg to 45 mg, indicating this dose is efficacious and well tolerated.
- A dose of 40 mg was shown to induce a 2-fold increase in histone 3 acetylation (acH3) in 17 subjects with solid tumors, a level comparable to that achieved with a dose ≥ 60 mg but significantly higher than achieved with a dose of 20 mg, suggesting that a dose of 45 mg may be sufficient for full pharmacodynamic effects.
- A dose of 45 mg results in plasma concentrations greater than HDAC C1 K_i for approximately 24 hours, suggesting adequate HDAC inhibition at this dose (data on file).

1.7 Rationale for Patient Population

The study will enroll only patients with high and very high-risk MDS by IPSS-R because this is a patient subset with the shortest overall survival and the most significant unmet need. Furthermore, in Study MEI-003, patients with high-risk MDS randomized to pracinostat plus azacitidine had a discontinuation rate similar to that observed with azacitidine plus placebo, whereas patients with intermediate-2 MDS had a higher discontinuation rate in the pracinostat + azacitidine group, suggesting a different level of tolerability to treatment toxicities.

2 STUDY OBJECTIVES

2.1 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
- Determine the overall response rate (ORR), defined as complete remission (CR) and partial remission (PR), of pracinostat plus azacitidine in high/very high-risk MDS

2.2 Secondary Objectives

Evaluate the following endpoints in patients with high/very high-risk MDS administered pracinostat plus azacitidine:

- CR rate
- Overall hematologic improvement (HI) rate
- Clinical benefit rate, defined as rate of CR + PR + HI + Marrow CR
- Rate of cytogenetic CR
- DoR
- Rate of leukemic transformation
- EFS
- PFS
- OS

3 STUDY DESIGN

This is a Phase 2, two-stage study of the safety and efficacy of pracinostat in combination with azacitidine in patients with IPSS-R high and very high-risk MDS who are previously untreated with HMAs. Enrollment in this study will be limited to high/very high-risk MDS because this group represents the highest unmet need, with median survival of less than 18 months. Recognizing that additional safety and efficacy of pracinostat plus azacitidine is desirable before evaluating the treatment regimen in a placebo-controlled environment, the protocol is being amended to become a 2-stage open-label study comprising Stage 1 and Stage 1 expansion (Stage 1b).

Stage 1 will be conducted as an open-label single arm in approximately 40 evaluable subjects to assess if the pracinostat dose regimen results in a discontinuation rate that meets a predefined threshold, and the observed efficacy justifies expansion of enrollment in Stage 1b.

A discontinuation rate of approximately ≤ 10% in Stage 1, a rate comparable to that observed with azacitidine alone in Study MEI-003, would support expansion to Stage 1b. Stage 1b will be conducted as an open-label arm to achieve a total enrollment of approximately 60 subjects evaluable for efficacy, inclusive of Stage 1 and Stage 1b enrollment.

Study drugs should be continued until disease progression or intolerable toxicity. It is important to note that the median time to achieving a response with azacitidine alone is 4 to 5 months. Therefore, early (< 6 months) discontinuation of study therapy for ‘no response’ should be avoided. The Medical Monitor should be contacted by the Investigator prior to discontinuing study drugs in a subject from the study to discuss the rationale for discontinuation.

After discontinuing study drugs, subjects will be followed every 3 months (± 1 month) until death or study termination to collect information on disease status (i.e., improvement of disease

response or disease progression), start of non-protocol therapies (e.g., stem cell transplant or an MDS-directed therapy) and survival.

The primary study analysis will be performed approximately 12 months after the last subject is enrolled in the study. The study duration is anticipated to be approximately 36 months: 24 months for enrollment and 12 months of follow-up until the primary analysis. At the completion of the primary analysis, the Sponsor will decide whether to terminate the study or continue study drug dosing in ongoing subjects.

It is anticipated that subject participation in the study will be for a median of approximately 10 cycles in the group receiving pracinostat + azacitidine.

3.1 Treatment Plan

3.1.1 Pracinostat

Pracinostat is supplied as 45-mg capsules and is self-administered orally (by the subject) once per day, 3 days each week for 3 weeks, followed by 1 week of rest, except on Day 1 of Cycle 1, when the study medication is to be administered at the clinic. Treatment cycles are repeated every 28 days, unless delayed due to toxicity.

Pracinostat is to be taken in the morning on an empty stomach or after a light meal with a full glass of water at approximately the same time each of the 3 days weekly (e.g., Monday, Wednesday, Friday). Subjects should be instructed to swallow the capsules whole and to not chew or crush them. Pracinostat is to be taken before administration of azacitidine. If vomiting occurs, no attempt should be made to replace the vomited dose. Pracinostat should not be taken with grapefruit, grapefruit juice, or Seville oranges (see Section 8.2).

The dosing interval between two consecutive doses of pracinostat should be approximately 48 hours. For example, if a subject forgets to take the dose before noon, it should be withheld that day and restarted the next day to ensure approximately 48 hours between each dose. As an additional example, if a subject misses a dose on Monday, the dose can be restarted on Tuesday, and the other doses would be taken on Thursday and Saturday.

Study medication compliance will be assessed by capsule counts on Day 1 of each cycle. The research staff are to count and document the amount of pracinostat taken and returned by the subject.

In later cycles (i.e., after Cycle 4), 45-mg pracinostat can be dose reduced to orally 3 days each week × 2 weeks (instead of 3 weeks) or dose interruption is allowed to manage toxicity such as fatigue, GI toxicity, or myelosuppression. Discuss with the Medical Monitor before decreasing pracinostat dosing from 3 to 2 weeks per cycle.

Subjects who are smokers are prohibited from smoking while receiving pracinostat because smoking induces cytochrome CYP1A2 and reduces pracinostat plasma concentrations by approximately 60% (see IB for information on the effect of smoking on pracinostat PK in Study MEI-006 in healthy volunteers). The effect on CYP1A2 is due to inhaled hydrocarbons

(including vaporizing e-cigarettes). As such, chewing tobacco and nicotine gum or patches are allowed. Subjects should be asked at site visits about any use of tobacco products.

3.1.2 Azacitidine

All subjects will receive a standard regimen of azacitidine at 75 mg/m^2 for 7 days of each 28-day cycle. Administration will occur by SC injection, or IV infusion if SC injections are not tolerated, on one of two schedules:

- Schedule 1 – daily therapy on Days 1 through 7
- Schedule 2 – 5-2-2 schedule in which subjects receive azacitidine for 5 consecutive days (Days 1 through 5) with rest on Days 6 and 7, and resume azacitidine dosing the first two days of the next week (Days 8 and 9) of each 28-day cycle.

Azacitidine should be given at approximately the same time each day. Each Investigator will declare preference as to which schedule is preferred for a subject and use that preference throughout the study. Please contact the Medical Monitor if a change in schedule is required.

The total dose will be calculated based on the subject's actual weight on Cycle 1 Day 1 (or up to 7 days before). The dose should be recalculated if the subject's weight changes by ≥ 10% during the study. Sites may follow their institutional guidance for assessing the weight used for dosing. In the presence of toxicity, azacitidine dose reduction in Cycle 2 and subsequent cycles will be performed according to the azacitidine product labeling recommendations or local standards of care.

4 SUBJECT POPULATION AND DISCONTINUATION CRITERIA

4.1 Inclusion Criteria

To be eligible for study participation, subjects must meet the following inclusion criteria:

1. Female or male subjects ≥ 18 years-of-age.

2. Histologically or cytologically documented diagnosis of MDS according to the World Health Organization (WHO) classification (Vardiman 2009, Arber 2016; Appendix B) with < 20% bone marrow blasts by morphology and a peripheral white blood cell (WBC) count of < 20,000/μL.

   - If WBC ≥ 20,000/μL, cytoreduction with hydroxyurea is permitted prior to enrollment.

   - CMML-1 and CMML-2 subtypes are eligible for study participation.

3. Classified as high or very high risk according to the Revised International Prognostic Scoring System (IPSS-R) risk category (Appendix C). CMML-1 and CMML-2 subtypes will be considered high-risk MDS and will not require IPSS-R scoring.
4. Bone marrow biopsy (BMBx) and/or aspirate within 28 days prior to planned first study treatment.

5. Clinical indication for treatment with azacitidine.
6. Previously untreated with HMAs (prior therapy with transfusions, hematopoietic growth factors, or immunosuppressive therapy is allowed).

    - Subjects who require start of an HMA (e.g., azacitidine) due to progressing MDS may receive up to 1 cycle of azacitidine within 30 days prior to Cycle 1 Day 1.

7. ECOG performance status of 0, 1, or 2.
8. Adequate organ function as evidenced by:

    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × the upper limit of normal (ULN).

    - Total bilirubin ≤ 1.5 × ULN or total bilirubin of ≤ 2 mg/dL, whichever is higher. Total bilirubin < 3 x ULN for patients with Gilbert-Meulengracht Syndrome.

    - Serum creatinine ≤ 1.5 x ULN, or creatinine clearance ≥ 40 mL/min according to institutional standards (actual body weight should be used to calculate creatinine clearance).

    - QTcF interval ≤ 450 msec using the mean of triplicate electrocardiograms (ECGs).

9. Female subjects of childbearing potential and male subjects with female partners of childbearing potential are required to use two forms of acceptable contraception, including one barrier method, during their participation in the study and for 30 days following last dose. Female subjects of childbearing potential must not be breastfeeding, or planning to breastfeed, and must have a negative pregnancy test ≤ 7 days before first study drug administration. Male subjects must also refrain from donating sperm during their participation in the study.
10. Voluntary written informed consent before performance of any study-related procedure not part of normal medical care.
11. Have the willingness and ability to understand the nature of this study and to comply with the study and follow-up procedures.

4.2 Exclusion Criteria

Exclude subjects from this study if they do not fulfill the inclusion criteria, or if any of the following criteria are observed:

1. Bone marrow blasts ≥ 20%, indicating a diagnosis of AML.
2. Received any of the following within the specified time frame prior to administration of study medication:

    - Any investigational agent within 14 days or 5 half-lives prior to enrollment, whichever is longer.

- Hydroxyurea within 48 hours prior to first day of study treatment.

- Hematopoietic growth factors: erythropoietin, granulocyte colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), or thrombopoietin receptor agonists at least 7 days (14 days for Aranesp), prior to study enrollment.

- Major surgery within 28 days prior to first study treatment.

3. Subjects who have not recovered from side effects of previous therapy.

4. Cardiopulmonary function criteria:

   - Current unstable arrhythmia requiring treatment.

   - History of symptomatic congestive heart failure (New York Heart Association [NYHA] Class III or IV).

   - History of myocardial infarction, pulmonary embolism or cerebrovascular accident within 6 months of enrollment.

   - Current unstable angina.

5. Prior treatment for MDS with the HDAC inhibitors Zolinza (vorinostat), Belenodaq (belinostat), Farydak (panobinostat), Istodax (romidepsin/depsipeptide), or investigational agent with significant action as an HDAC inhibitor.

6. Clinical evidence of central nervous system involvement.

7. Subjects with GI tract disease causing the inability to take oral medication, malabsorption syndrome, a requirement for IV alimentation, prior surgical procedures affecting absorption, uncontrolled inflammatory GI disease (e.g., Crohn's disease, ulcerative colitis).

8. Uncontrolled infection with human immunodeficiency virus (HIV) or chronic hepatitis B or C.

9. Life-threatening illness unrelated to cancer or any serious medical or psychiatric illness that could, in the Investigator's opinion, potentially interfere with participation in this study.

10. Presence of a malignant disease within the last 12 months, with the exception of adequately treated in-situ carcinomas, basal or squamous cell carcinoma, non-melanomatous skin cancer, or malignancies treated with curative intent and no evidence of active disease in prior 12 months and felt to be low risk for recurrence. Other malignancies may be considered after consultation with the Medical Monitor.

11. An unwillingness or inability (including breastfeeding women, prohibited concomitant medications, uncontrolled infections, psychological, familial, sociological, or geographical conditions) to comply with study and/or follow-up procedures as outlined in the protocol.

12. Known hypersensitivity to any components of pracinostat, azacitidine or mannitol.

13. Current smoking or vaporizing of tobacco or cannabis-related products (use of patches, chewing tobacco, or nicotine gum is permitted). Subjects who stopped smoking at least 8 days prior to first pracinostat dosing can be enrolled, provided they refrain from smoking during the whole study.

4.3 Discontinuation from Study Treatment

The Medical Monitor should be contacted prior to discontinuation of study treatment.

Subjects will be discontinued from study treatment for any of the following reasons:

- Documented disease progression or relapse after CR/PR by the International Working Group (IWG) criteria (see Section 5.2.4). Because subjects with MDS receiving HMAs may require more than 6 cycles of therapy to achieve a response (median 4 to 5 cycles), discontinuation due to "lack of response" in the first 6 cycles of therapy must be avoided.
- Decision to proceed to intensive therapy and stem cell transplant.
- Irreversible or intolerable toxicity or abnormal and clinically significant laboratory values thought to be related to drug toxicity and not manageable by supportive approaches and/or study drug dose reduction or interruption.
- Pregnancy.
- Subject request to withdraw from treatment or from the study.
- Conditions requiring therapeutic intervention not permitted by the protocol.
- Lost to follow-up.
- Non-compliance with study treatment or study-related assessments that compromise the proper evaluation of the patient's safety.
- Early study termination by the Sponsor, the Sponsor's designee, or regulatory authorities.

After discontinuation from protocol treatment, subjects must be followed for AEs for 30 calendar days after their last dose of study medication. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the Investigator, these AEs are not likely to improve because of the underlying disease.

All subjects who have Grade 3 or 4 laboratory abnormalities (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.03) at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2, unless it is, in the opinion of the Investigator, not likely that these values will improve.

5 STUDY PROCEDURES AND ASSESSMENTS

See the Schedule of Assessments (Appendix A) for a complete list of all study procedures and assessments.

5.1 Screening

The Screening visit should occur ≤ 14 days prior to first study treatment. Physical examinations and serum chemistries on Day 1 do not need to be repeated if performed within 7 days prior to Day 1.

The following procedures and assessments will be performed during screening:

- Written informed consent must be obtained prior to initiating any other study-required procedure. Some tests performed prior to obtaining informed consent (e.g., bone marrow biopsy) may not need to be repeated for this study as long as they were performed within the allowed window described in this protocol. This window allows subjects to not unnecessarily repeat tests and impose an undue burden to them.
- Determine eligibility including IPSS-R score for enrollment.
  - Note: IPSS score for subjects enrolled under Amendment 2 will also be calculated for comparison with historical data, however IPSS will not be used to determine eligibility (Appendix C).
- Medical history, including recent smoking history.
- Transfusion history for 8 weeks prior to first study drug administration.
- Physical examination.
- Vital signs, including height, weight, blood pressure, resting heart rate, and oral temperature.
- ECOG performance status determination (see Appendix E).
- Baseline signs and symptoms.
- AE/toxicity assessment.
- Concomitant medication review.
- 12-lead ECG in triplicate, approximately once every 2 to 5 minutes to calculate the QTcF interval.
- Two complete blood counts (CBCs) with differential and blasts ≥ 7 days apart within 1 month prior to first study drug administration; the second CBC may be obtained on Cycle 1 Day 1 prior to first study drug administration. For this study, a CBC will consist of, at a minimum, WBC count with differential, absolute neutrophil count (ANC), lymphocyte count, red blood cell (RBC) count and indices, hemoglobin, hematocrit, platelets, and blast count where applicable.

- Serum chemistry: glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, calcium, carbon dioxide (CO_2), alkaline phosphatase (ALP), AST, ALT, total bilirubin, total protein, albumin, and lactate dehydrogenase (LDH).

- Serum pregnancy test for women of child-bearing potential (must be performed within 7 days of first study treatment).

- Bone marrow biopsy and aspiration within 28 days prior to planned first study treatment.

5.2 Study Treatment

Study visits should occur on a 28-day schedule. A -4 day to +7-day window is allowable for each clinic visit to accommodate subject request, holidays, weekends, inclement weather, or other unforeseen circumstances.

Pracinostat is to be taken in the morning on an empty stomach or following a light meal once a day on Days 1, 3, and 5 (Week 1); Days 8, 10, and 12 (Week 2); and Days 15, 17, and 19 (Week 3); with a week of rest during Week 4. Pracinostat will be administered in the clinic on Day 1 of Cycle 1, and subjects may self-administer at home on all other days. Pracinostat is to be taken before azacitidine. Missed doses of pracinostat should not be made up (refer to Section 3.1.1). To monitor pracinostat dosing, subjects will be given a dosing diary card to track medication compliance.

5.2.1 Day 1, All Cycles

The following procedures and assessments will be performed on Day 1:

- Update of transfusion history for 8 weeks prior to first study drug administration on Cycle 1 Day 1 only

- Physical examination

- Vital signs

- Smoking assessment (for subjects enrolled under Amendment 1)

- ECOG performance status determination

- AE assessment

- Concomitant medication review

- 12-lead ECG performed in triplicate approximately once every 5 to 10 minutes to calculate the QTcF interval. On Day 1 of Cycle 1, ECGs will be obtained pre-dose, pracinostat will be taken, and azacitidine will be administered. Ninety minutes (± 15 minutes) post-pracinostat dosing, triplicate ECGs will be repeated. Beyond Cycle 1, non-triplicate ECGs will be performed as clinically indicated.

- Administer pracinostat.
- CBC with differential and blasts.
- Serum chemistry: glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO_2, ALP, AST, ALT, total bilirubin, total protein, albumin, and LDH.
- Dispense study medication. Following Cycle 1, study medication compliance will be assessed on Day 1 of each cycle.
- Azacitidine administration.
- Response assessments (after Cycle 2 and Cycle 6; see Section 5.2.4).

5.2.2 Days 2–9, All Cycles

- AE assessment on each day of azacitidine administration.
- Azacitidine administration (see Section 3.1.2).

5.2.3 Day 15 and Day 22 (Cycles 1 and 2 only)

- Vital signs.
- Smoking assessment (for subjects enrolled under Amendment 1).
- AE assessment.
- Concomitant medication review (Day 22 only).
- CBC with differential and blasts. A manual differential is preferred but is not required at these visits.
- Serum chemistry: glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO_2, ALP, AST, ALT, total bilirubin, total protein, albumin, and LDH.

5.2.4 Response Assessments

To assess hematologic response, CBC with differential including blast cell counts will be obtained every Cycle Day 1 (-4 days to +7 days), and when response assessments and confirmations are scheduled to be performed (Appendix A).

A BMBx and aspirate to assess cellularity, blast percentage, morphology (dysplasia), and cytogenetics (if abnormal at baseline), as well as a CBC with differential will be required at the end of Cycles 2 and 6, with evidence of disease progression, with evidence of hematologic CR which may occur after Cycle 6, and prior to transplant if the subject becomes a candidate for transplant. Once a marrow CR is documented, there is no need to repeat a BMBx unless clinically indicated.

Ideally, transplant will be after the conclusion of ≥ 4 cycles of therapy. The following assessments are to be performed, and the Medical Monitor is to be advised of the results prior to discontinuing treatment for transplant:

- Bone marrow biopsy and aspiration (classic cytogenetics, fluorescence in-situ hybridization [FISH], and molecular studies, if done at baseline).*
- CBC with differential and blasts.

* FISH and molecular studies are not required by protocol, but results should be collected in the electronic data capture (EDC) system if performed as per local practice.

Transfusions in the 8 weeks prior to starting study drugs and while on study and hematopoietic growth factor use will also be captured to assess efficacy.

Local (i.e., Investigator) assessments of response will be utilized for the primary efficacy analyses, employing the IWG standardized response criteria for evaluating clinically significant responses in MDS (Cheson 2006). These criteria measure alterations in the natural history of disease, hematologic improvement, cytogenetic response, and improvement in health-related quality of life. Diagnosis of MDS according to the WHO classifications are presented in Appendix B.

The IWG Response Criteria for MDS are presented in Appendix D. The response categories are as follows:

- CR
- PR
- Marrow CR
- HI
- Stable Disease
- Failure
- Relapse after CR or PR
- Cytogenetic Response
- Disease Progression
- Survival

A CBC with differential will be required for confirmation of CR or PR 8 weeks following the initial report of response.

Modified IWG response criteria are presented in Appendix D.

5.3 End of Treatment

End of Treatment evaluations are required no less than 7 days and no more than 30 days after treatment ends, or prior to starting new treatment if urgent treatment is required due to disease progression.

The following assessments will be performed:

- Smoking assessment (for subjects enrolled under Amendment 1).
- ECOG performance status determination.
- AE assessment.
- Concomitant medication review.
- Bone marrow biopsy and aspirate must be performed if a subject discontinues due to disease progression without clear evidence of progression by peripheral blood counts, due to an AE, or prior to bone marrow transplant. This is required if a BMBx and aspirate have not been obtained within 56 days prior to study discontinuation. Bone marrow cytogenetics will be performed if the subject discontinues the study in CR to confirm a cytogenetic CR (unless cytogenetic CR has been confirmed in previous marrow assessments).
- CBC with differential and blasts count.
- Serum chemistry: glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO_2, ALP, AST, ALT, total bilirubin, total protein, albumin, and LDH.
- Study medication compliance assessment (if applicable).

5.4 Follow-up

After subjects discontinue study drug, they will be followed every 3 months (± 1 month) until death or study termination to collect information on progression, any new treatments, and survival (e.g., date and cause of death). With suspicion of disease progression, a CBC (including 3-part differential, platelets, and blasts) may be performed (optional). Subjects may be contacted during outpatient visits or by telephone.

5.5 End of Study

The end of this study occurs when the Sponsor terminates the study when sufficient subject follow-up has been obtained, anticipated to occur approximately 12-months after follow-up of the last subject enrolled plus the time to complete End of Treatment evaluations. The Sponsor or designee reserves the right to temporarily suspend or terminate the study at any time for reasons including, but not limited to, safety issues or ethical reasons.

5.6 Cytogenetic and Molecular Studies

Classical cytogenetics shall be required with BMBx and aspirate, and peripheral blood samples taken as part of the standard of care. Fluorescence in situ hybridization (FISH) and molecular tests (e.g., polymerase chain reaction) may be conducted as per standard of care but are not required. If FISH or molecular tests are performed as part of the patient's local standard of care, the data should be documented in the case report form (CRF).

6 SAFETY

Safety assessments will consist of monitoring and recording protocol-defined AEs and serious AEs (SAEs), measurement of protocol-specified hematology, clinical chemistry, measurement of protocol-specified vital signs, and other protocol-specified tests that are deemed critical to the safety evaluation of the study medication.

Investigators must report SAEs and follow-up information to their responsible Institutional Review Board (IRB) or ethics committee (EC) according to the policies of the responsible IRB/EC.

6.1 Adverse Events

6.1.1 Definitions of Adverse Events

An AE is the development of an undesirable medical condition, or the deterioration of a preexisting medical condition following or during exposure to a medicinal product, whether or not considered causally related to the product.

An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver), or the abnormal results of an investigation (e.g., laboratory findings).

6.1.2 Recording and Reporting of Adverse Events

All AEs regardless of seriousness or relationship to pracinostat or azacitidine, from the start of study drug treatment until 30 calendar days after discontinuation or completion of treatment as defined by the clinical study for that subject, are to be recorded in the CRF. The Investigator will provide an opinion as to the relationship of the AE to the study drug treatment (i.e., the event is related or unrelated to study medication administration).

All AEs should be documented. A description of the event, including date of onset and resolution, any relevant SAE outcome criteria, any action taken (e.g., changes to study treatment), and outcome, should be provided along with the Investigator's assessment of causality (i.e., the relationship to the study treatment[s]). For an AE to be a suspected treatment-related event there should be at least a reasonable possibility of a causal relationship between the protocol treatment and the AE. Adverse events will be graded according to the NCI CTCAE v4.03, and changes will be documented.

To ensure consistency of AE and SAE causality assessments, Investigators should apply the following general guideline:

YES: There is a plausible temporal relationship between the onset of the AE and administration of the study treatment, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the study treatment; and/or the AE abates or resolves upon discontinuation of the study treatment or dose reduction and, if applicable, reappears upon re-challenge.

NO: Evidence exists that the AE has an etiology other than the study treatment (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to study treatment administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected AEs are those that are listed or characterized in the current version of the pracinostat IB.

If the AE is serious, it should be reported immediately; refer to Section 6.2.2 for SAE reporting requirements and contact information. Other untoward events occurring in the framework of a clinical study are also to be recorded as AEs (i.e., AEs that occur prior to assignment of study treatment and after the signing of the informed consent form (ICF), that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

Any clinically significant signs and symptoms; abnormal test findings; changes in physical examination; hypersensitivity; and other measurements that occur will be reported as an AE.

Laboratory results or test findings will be reported as an AE if the test result requires an adjustment in the study medication(s) or discontinuation of treatment; and/ or test findings require additional testing or surgical intervention; a test result or finding is associated with accompanying symptoms; or a test result is considered to be an AE by the Investigator.

6.1.3 Handling of Adverse Events

All AEs should be followed until resolution or stabilization. Subjects must be followed for AEs for 30 calendar days after discontinuation or completion of research study-specific treatment (e.g., chemotherapy, radiation, oral medications, targeted therapy, and surgery) or until the initiation of new therapy for MDS. All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the Investigator, the AE or laboratory abnormality/ies are not likely to improve because of the underlying disease.

All adverse events occurring from signing of informed consent to 30 calendar days after completion or discontinuation of protocol-specific treatment, are to be recorded on the appropriate eCRF section.

Once > 30 days have elapsed, only AEs, SAEs, or deaths assessed by the Investigator as treatment-related are to be reported.

6.2 Serious Adverse Events

The Investigator is responsible for recognizing and reporting SAEs as outlined in this section. It is the Sponsor or designee's responsibility to report relevant SAEs to the applicable local, national, or international regulatory bodies.

6.2.1 Definitions of Serious Adverse Events

An SAE is defined as any untoward medical occurrence that:

- results in death
- is immediately life-threatening
- requires at least a 24-hour inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect.

The definition of SAE also includes any important medical event. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the previous definition. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

"Disease progression" or "relapse from remission" as such, should not be reported as an SAE.

Treatment within or admission to the following facilities is not considered to meet the criteria of "inpatient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency Department or Emergency Room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, Custodial care or Respite care facility

Hospitalization during the study for a pre-planned surgical or medical procedure (one which was planned prior to entry in the study), does not require reporting as an SAE.

6.2.2 Serious Adverse Event Reporting by Investigators

It is important to distinguish between "serious" and "severe" AEs, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. For example, nausea which persists for several hours may be considered severe nausea but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke but would be considered an SAE. Severity and seriousness should be independently assessed when recording AEs and SAEs.

Adverse events classified by the treating Investigator as serious require expeditious handling and reporting in order to comply with regulatory requirements. Serious AEs may occur at any time from the start of study treatment through the 30-day follow-up period after the last study treatment. All SAEs, regardless of causality, must be reported within 24 hours of when the Investigator is first informed of the event and followed until resolution (with autopsy report, if applicable). Serious AEs that occur prior to assignment of study treatment, that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, are to be reported.

All SAEs, regardless of causality, must be entered in the eCRF and supporting documentation (i.e., hospital records, autopsy reports) must be reported to:

Clinipace Worldwide
Fax: (919) 573-9526
Email: MEI16011.safety@clinipace.com

MEI Pharma – Medical Monitor
Phone: primary (David Ramies, MD): (925) 285-6640;
back-up (Richard Ghalie, MD): (619) 990-1153

Deaths and other SAEs occurring > 30 calendar days after last study treatment that are deemed related (causality = YES) to pracinostat must be reported as SAEs within 24 hours of when the Investigator is first informed of the event. Whenever possible, an autopsy report should be collected.

Deaths occurring > 30 calendar days after last study treatment and not attributed to study treatment (e.g., disease progression) need not be reported as SAEs, but should be collected as part of the study data.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported as soon as it is available. Refer to the study reference manual for detailed SAE reporting guidelines.

Investigators must report SAEs and follow-up information to their responsible IRB/EC according to its policies.

6.2.3 Sponsor Serious Adverse Event Reporting Requirements

The Sponsor or designee is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating Investigators, in accordance with the International Council on Harmonisation (ICH) guidelines, FDA regulations, and/or local regulatory requirements.

6.3 Recording of Adverse Events and Serious Adverse Events

6.3.1 Diagnosis versus Signs and Symptoms

All AEs should be recorded individually unless the AEs constitute components of a recognized condition, disease, or syndrome. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate. If a diagnosis is subsequently established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

6.3.2 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between subject evaluation time points. Such events should only be recorded once. If a persistent AE becomes more severe or lessens in severity, it should be recorded separately.

A recurrent AE is one that occurs and resolves between subject evaluation time points, and subsequently recurs. All recurrent AEs should be recorded.

6.3.3 Abnormal Laboratory Values

If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE or SAE, and the associated laboratory value or vital sign should be considered additional information that must be collected. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis should be recorded.

Abnormal laboratory values will be reported as an AE if the laboratory result requires an adjustment in the study medication(s) or discontinuation of treatment; and/ or laboratory findings require additional testing or surgical intervention; a laboratory result or finding is associated with accompanying symptoms; or a laboratory result is considered to be an AE by the Investigator.

6.3.4 Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the Investigator solely to progression of disease should be recorded in the Death Report CRF.

All other on-study deaths, regardless of attribution, will be recorded as an SAE and expeditiously reported.

When recording an SAE with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept.

6.3.5 Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization of > 24 hours or prolongation of preexisting hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalizations that do not require reporting as an SAE (see Section 6.2.1).

6.3.6 Preexisting Medical Condition

A preexisting medical condition is one that is present at the start of the study. Such conditions should be recorded as part of the subject's medical history. A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors.

6.3.7 New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the serious criteria (see Section 6.2.1). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the subject into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered disease progression.

6.4 Adverse Events of Special Interest

Adverse Events of special interest (AESI) are defined as pre-specified AEs, serious and non-serious, under ongoing monitoring by the Sponsor. No specific reporting timelines or other activities are required by the Investigator in addition to the normal AE reporting practices as described in the above sections for the following AESIs:

- Supraventricular arrhythmias
- Sepsis, septic shock, Grade ≥ 3 lung infection (pneumonia)
- Any infection leading to death
- Grade ≥ 3 anemia, neutropenia, febrile neutropenia, and thrombocytopenia
- Grade ≥ 3 hemorrhage

6.4.1 QTc Prolongation

Any QTc prolongation ≥ 500 ms and/or > 60 ms change from baseline, irrespective of the relationship to study treatment, must be always reported as an AE (see Section 6.1.2).

The Investigator or the Investigator's designee must complete the AE pages of the eCRF with all necessary information, and any accompanying source documents (hospital records, ECG report, etc.) should be faxed or e-mailed (as PDFs) at the following contacts:

Clinipace Worldwide
Fax: (919) 573-9526
Email: MEI16011.safety@clinipace.com

6.4.2 Pregnancy, Abortion, Birth Defects/Congenital Anomalies

Female subjects of child-bearing potential and male subjects (even if surgically sterilized) must:

- Agree to practice effective barrier contraception during the entire study treatment period and for 30 days following last dose, or
- Agree to completely abstain from heterosexual intercourse.
- Male subjects must also refrain from donating sperm during their participation in this study.

During the course of the study, all female subjects of childbearing potential (the definitions of "women of childbearing potential" are listed in Appendix G) must contact the treating Investigator immediately if they suspect that they may be pregnant (a missed or late menstrual period should be reported to the treating Investigator).

If an Investigator suspects that a subject may be pregnant after the subject has been receiving study medications, study drugs must immediately be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, study drugs must be immediately and permanently stopped, the subject must be discontinued from the study, and the Investigator must notify the Sponsor/designee as soon as possible.

If a subject becomes pregnant while enrolled in the study, the Investigator should expeditiously report this event, regardless of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported. Refer to Appendix G for detailed information on the pregnancy reporting process.

6.4.3 Pracinostat Overdose

There is no specific antidote to pracinostat. If overdose is suspected, administration of study drug should be stopped, and general supportive measures instituted. The risk of overdose is minimized by the standard dose and written dosing instructions for subjects.

Symptomatic and non-symptomatic overdose (e.g., > 45 mg single dose or > 2 doses in a < 48-hour interval) must be collected as part of the study data. Any accidental or intentional

overdose with the study drug that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported within 24 hours from first knowledge of the event and following the same process described for SAE reporting (see Section 6.2.2).

6.5 Study Drug Dose Modifications

Adverse events and laboratory abnormalities (see Appendix A for details) will be monitored throughout the study and toxicities will be graded per NCI CTCAE v4.03. Appropriate supportive care treatment, such as antiemetics or antidiarrheal treatment, will be administered according to local standards of care as appropriate, prior to considering study drug dose modification or interruption.

If necessary to manage toxicities, azacitidine dose reduction will be implemented according to its package insert or local standards of care. Pracinostat dose reduction to less than 45 mg is not planned in this study. Of note, there may be overlapping toxicities between azacitidine and pracinostat, particularly for myelosuppression, fatigue, nausea, and vomiting.

6.5.1 Dose Modification or Interruption for Non-Hematologic Toxicity

From Cycle 2 onwards in case of Grade ≥ 3 non-hematologic toxicities a dose reduction or, as a subsequent option, a dose interruption of both pracinostat and azacitidine is permitted after prior discussion with the Medical Monitor.

Patients with Grade ≥ 3 non-hematologic toxicities may have both study drugs held up to a maximum of 4 weeks, or until return to Grade 1 or baseline (whichever comes first). However, in patients who are experiencing a reduction in marrow blasts but have not achieved counts < 5%, dose interruptions beyond 28 days are permitted, but require prior discussion with the Medical Monitor.

- If unexplained reductions in serum bicarbonate levels (or CO_2 if bicarbonate is not routinely measured at the site) to < 20 mmol/L occur, then the azacitidine dose should be reduced by 50% for all subsequent cycles.

- If unexplained elevations of urea/BUN or serum creatinine to ≥ 2-fold above baseline values and above ULN occur, then the next cycle should be delayed until values return to normal or baseline, and the azacitidine dose should be reduced by 50% for all subsequent cycles.

- When a QT prolongation is observed for the first time, the patient should be followed with additional ECGs as determined by the Investigator. All study drugs should be held until QT returns to baseline in patients who develop any of the following, unless there is a clear alternative cause for the changes:

    - Sustained (at least two ECG measurements, approximately 30 minutes apart) QTcF that is ≥ 500 ms and/or > 60 ms longer than the baseline value.

    - New ECG finding of clinical concern.

Study drugs may be resumed, provided that any ECG abnormalities have been resolved, and underlying causes have been addressed, the patient remains clinically stable and is appropriately monitored. Clinical judgment should be applied.

6.5.2 Dosage Adjustments of Study Drugs

Subjects will receive one course of therapy during every 28-day cycle. The Medical Monitor will review with the Investigator any decision to reduce or discontinue either of the study drugs (pracinostat or azacitidine).

In the presence of toxicity, azacitidine dose reduction must be implemented according to its package insert or local standards of care. Azacitidine dose reduction is not allowed in Cycle 1 but may be implemented in Cycle 2, if deemed clinically necessary.

If after Cycle 4 the subject experiences continued toxicity despite azacitidine dose reduction, then the schedule of pracinostat administration may be reduced as presented in Table 1. Please discuss with the Medical Monitor before reducing the dose of pracinostat from 3 to 2 weeks per cycle.

Table 1 Pracinostat Dose Level Modifications

Dose Level	Pracinostat
Starting Dose	45 mg administered orally once a day, 3 days each week (e.g., Monday, Wednesday, Friday) for 3 consecutive weeks, followed by 1 week of rest, in 28-day cycles
Dose Level -1	45 mg administered orally once a day, 3 days each week (e.g., Monday, Wednesday, Friday) for 2 consecutive weeks, followed by 2 weeks of rest, in 28-day cycles

7 STUDY DRUG

7.1 Study Drug

Investigational Product	Dosage Form and Strength
Pracinostat	45-mg capsules

7.1.1 Study Drug Labeling, Packaging, and Supply

Pracinostat 45-mg capsules will be supplied by MEI Pharma.

All study drugs must be kept in a secure place under appropriate storage conditions. Pracinostat capsules should be stored at controlled room temperature, 20 – 25°C (68 – 77°F) with excursions allowed between 15 – 30°C (59 – 86°F).

7.1.2 Preparation and Administration of Study Drug

No preparation of pracinostat is necessary.

Details of pracinostat administration are provided in Section 3.1.1.

7.1.3 Accountability of Study Drug

The Investigator (or designee) is responsible for accountability of all used and unused study medication supplies at the site.

The Sponsor or its representatives must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

All study drug inventories must be made available for inspection by the monitor, the Sponsor (or its designees), and regulatory agency inspectors upon request.

At the end of the study, study drug will be returned to the Sponsor (or designee) or destroyed. Study drug must not be destroyed unless prior approval has been granted by the Sponsor or its representative.

7.1.4 Precautions and Risks Associated with the Study Drug

Precautions and associated risks with pracinostat	
Hematologic	Treatment with pracinostat has been associated with cytopenias including anemia, thrombocytopenia, and neutropenia. The incidence of cytopenias may increase with increasing doses of pracinostat. Subjects participating in clinical studies of pracinostat should be monitored closely for adverse hematologic affects. The effect of dose reduction on the amelioration of cytopenias has not been established, however prudent clinical management, including supportive care (appropriate use of transfusions and/or hematopoietic growth factors) and dose modification or discontinuation should be followed (see Section 6.5).
Gastrointestinal	Gastrointestinal disturbances (including nausea, vomiting, and diarrhea) have been reported in subjects treated with pracinostat. Standard antiemetic and antidiarrheal medications and appropriate supportive care should be used per normal clinical practice in subjects participating in clinical studies of pracinostat. Preexisting nausea, vomiting, and diarrhea should be adequately controlled before beginning therapy.
QTc Prolongation/Cardiac	Asymptomatic QTc interval prolongation has been observed during clinical studies of pracinostat. Subjects with a CTCAE Grade 2 prolonged QTc interval during screening will not be permitted to participate in clinical studies of pracinostat. Hypokalemia or hypomagnesemia should be corrected prior to pracinostat administration and consideration should be given to monitoring potassium and magnesium in symptomatic subjects (e.g., subjects with nausea, vomiting, diarrhea, fluid imbalance, or cardiac symptoms). See the Investigator's Brochure for additional information on QTc prolongation. Concomitant medications with a known risk of prolonging the QT interval and/or causing Torsades de Pointes are prohibited. In addition, caution should be taken when using concomitant medications with a possible or conditional risk of prolonging the QT interval and/or causing Torsades de Pointes; medications with a possible or conditional risk may be used at the discretion of the Investigator (Appendix H).

Precautions and associated risks with pracinostat	
General Signs and Symptoms	Fatigue has been the most common AE reported in subjects receiving pracinostat and has frequently prompted dose reduction in subjects receiving > 60 mg/day. Anorexia has also been commonly reported. Subjects experiencing debilitating fatigue or anorexia with weight loss may benefit from dose reduction or interruption of pracinostat treatment. Related SAEs of febrile neutropenia fatigue, and pneumonia have been reported. Disturbances of the GI tract, including nausea, vomiting, and diarrhea, have been reported in patients treated with pracinostat. In the Phase II study of pracinostat + azacitidine in AML, nausea, diarrhea and vomiting were among the most frequently reported manifestations of GI toxicity, with most cases graded as 1 or 2. Standard antiemetic and antidiarrheal medications and appropriate supportive care should be used per normal clinical practice. Pre-existing nausea, vomiting, and diarrhea should be adequately controlled before starting study drug.

Please refer to the IB for detailed information on the risks associated with the use of pracinostat.

7.2 Azacitidine

Azacitidine is to be administered in accordance with the terms of its marketing authorization and/or in accordance with local standards of care. Please refer to the approved Prescribing Information for detailed information on how to prepare and administer azacitidine.

7.2.1 Azacitidine Labeling, Packaging, and Supply

Where applicable, each site will procure a supply of azacitidine, which is commercially available.

All study medications must be kept in a secure place under appropriate storage conditions. Refer to the approved Prescribing Information for azacitidine storage conditions. The expiration date on the label must not be exceeded.

The Sponsor or its representatives must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

7.2.2 Preparation and Administration of Azacitidine

Azacitidine is to be prepared and administered in accordance with the terms of its marketing authorization or in accordance with local standards of care. For those sites unable to administer azacitidine according to the recommended administration schedule (for 7 consecutive days), a 5-2-2 administration scheme (5 consecutive days, 2 rest days, and the first 2 days of the following week) is acceptable. Azacitidine should be administered at approximately the same time each day. Each Investigator will declare preference as to which schedule is preferred for a subject and use that schedule throughout the study for this subject.

7.2.3 Precautions and Risks Associated with Azacitidine

Common risks associated with azacitidine administration	
Anemia, neutropenia, and thrombocytopenia	Perform CBCs prior to each treatment cycle and as needed to monitor response and toxicity.
Hepatotoxicity	Use with caution in subjects with severe preexisting liver impairment.
Renal abnormalities	Monitor subjects with renal impairment for toxicity since azacitidine and its metabolites are primarily excreted by the kidneys.

Monitor liver chemistries and serum creatinine prior to initiation of therapy and with each cycle.

Please refer to the approved Prescribing Information for detailed information on the risks associated with the use of azacitidine.

8 CONCOMITANT MEDICATIONS

Concomitant medications will be recorded from the first study drug administration until 30 days after the last study drug administration, or until new treatment for MDS is started.

8.1 Permitted Concomitant Medications

Premedication with antiemetics is allowed according to standard practice guidelines and/or local standards of care.

Prophylaxis with quinolone antibiotics is permitted per local standards of care.

Caution should be taken in concomitant administration of the following:

- Fibrinolysis inhibitors
- Anticoagulant and antiplatelet drugs

Other medications considered necessary for subject safety and well-being may be given at the discretion of the Investigator with the exception of those listed in Section 8.2.

8.2 Prohibited Concomitant Medications

The following treatments are prohibited while in this study:

- No other investigational therapy should be given to subjects.
- No anticancer agents should be administered to subjects. If such agents are required, the subject must first be withdrawn from the study.
- HDAC inhibitors (Zolinza [vorinostat], Istodax [romidepsin/depsipeptide]) or valproic acid (which has significant action as a HDAC inhibitor).

- Medications with a known risk of prolonging the QT interval and/or causing Torsades de Pointes.

- Herbal preparations (e.g., St John's wort) are not allowed throughout the study. Subjects must discontinue herbal medications at least 7 days prior to the first dose of study treatment.

- Patients should avoid grapefruits, grapefruit juice, and Seville oranges during the study since they are known to be inhibitors of CYP3A4.

- Smoking or vaporizing of tobacco or cannabis-related products is prohibited. These products must be discontinued at least 8 days prior to the first dose of study treatment. [Note: Nicotine gum or patches are allowed, as is chewing tobacco].

- Prophylactic G-CSF may be used only in subjects with a treatment-emergent AE of febrile neutropenia while on study, or in subjects with persistent (> 5 days) Grade 4 neutropenia who are at high risk for development of febrile neutropenia.

8.3 Medications/Agents Affecting Metabolism via Cytochrome P450

Limited clinical information is available on drug interactions for pracinostat. Pracinostat is a substrate of cytochrome P450 1A2 (CYP1A2), cytochrome P450 2C8 (CYP2C8) and cytochrome P450 3A4 (CYP3A4). Caution in use of pracinostat is required with drugs that inhibit 3A4 and 2C8 or induce CYP1A2, 2C8 and 3A4 (see Study PRAN-17-14 [Investigator's Brochure]). Lists of 3A4 and 2C8 inhibitors and 1A2, 2C8 and 3A4 inducers are provided in Appendix I.

Smoking results in CYP1A2 induction and has been shown to decrease pracinostat C_{max} and AUC by approximately 60%. Therefore, current smokers are excluded from the study.

9 STATISTICAL PLAN

9.1 Sample Size

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.

9.1.1 Sample Size Calculation for Stage 1

The goal of Stage 1 is to establish if this pracinostat + azacitidine regimen achieves a discontinuation rate of approximately ≤ 10% in the first 3 cycles of therapy, a rate comparable to that achieved in the azacitidine + placebo group in Study MEI-003. The 95% CI approach is utilized to estimate the sample size in Stage 1. The number of subjects to be enrolled is calculated such that the lower bound of the 95% CI of the discontinuation rate will be no more than 12% lower than the point estimate of 22.5%, the midpoint between the discontinuation rates in the azacitidine + placebo (10%) and azacitidine + pracinostat (32%) groups, respectively, in Study MEI-003.

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) and the upper bound of the 95% CI is > 32% (higher than the discontinuation rate in study MEI-003).

It is also possible to conclude that the desired threshold of a discontinuation rate of ≤ 10% has been achieved with fewer than 40 subjects treated in Stage 1. For example, if 4 discontinuations are observed in the first 32 subjects, the lower and upper bounds of the 95% CI around the observed discontinuation rate of 12.5% (4 of 32) are 3.5% and 29.0%, lower than reported with azacitidine/placebo and azacitidine/pracinostat, respectively, in Study MEI-003. This would justify expanding enrollment to Stage 1b of the study after only 32 subjects have been treated for ≥ 3 cycles.

In addition to the discontinuation threshold, an observed ORR of ≥ 20% will be desired to support opening Stage 1b of the study because it is expected that azacitidine alone results in an ORR of approximately 20% in high/very high-risk MDS.

The study's Independent Data Monitoring Committee (IDMC), in coordination with the Sponsor, will determine when enrollment in Stage 1 can be concluded, and whether to open enrollment in Stage 1b.

9.1.2 Total Sample Size Calculation

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 in higher risk MDS (Fenaux 2009, Prebet 2014, Sekeres 2014). 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 45% 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 higher risk MDS. Table 2 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%.

Table 2 Lower Bound of the 95% Confidence Interval for a Range of Overall Response Rate

	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%	18.9	22.0

CI = confidence interval; ORR = overall response rate.

9.2 Analysis Populations

The primary efficacy analysis will be conducted using the ITT population, which is defined as all treated subjects. Exploratory analyses will be performed for the Per-Protocol population, defined as subjects who received at least 2 cycles of therapy and a follow-up bone marrow assessment.

The Safety population, defined as all subjects who have been treated, will be used for the safety analysis.

9.3 Statistical Analysis

All analyses will be descriptive. Binomial variables will be presented as frequency and 95% CI. Continuous variables will be presented as median, mean, range, and 95% CI. Time-to-event endpoints will be analyzed according to the method of Kaplan-Meier.

Primary and exploratory analyses will be performed as described in detail in the study Statistical Analysis Plan.

9.3.1 Efficacy Analysis Endpoints

Efficacy endpoints include:

- Overall response rate (ORR), defined as the proportion of subjects with confirmed CR and PR according to the IWG criteria.

- Complete remission (CR) rate, defined as the proportion of subjects with confirmed CR (i.e., 2 CRs at least 28 days apart) according to the IWG criteria. Subjects who are not evaluable for response for any reason at or before the Cycle 6 response assessment will be considered as not achieving CR.

- Overall HI rate, defined as the proportion of subjects who demonstrate major hematologic improvement as defined by the IWG criteria. Only subjects with pre-treatment abnormal values will be considered for this endpoint at 8 weeks.

- Clinical benefit rate (CBR), defined as the proportion of subjects with confirmed CR, PR, Marrow CR, and HI. All patients who achieve hematologic CR, PR, marrow CR, or HI on the erythrocytic lineage (HI-E) per modified IWG response criteria will be considered responders.

- Rate of cytogenic complete response/remission, defined as the proportion of subjects with confirmed CR by cytogenetic assessment. Complete cytogenetic response is defined per modified IWG response criteria.

- Duration of response (DoR), for subjects who have achieved CR, PR, Marrow CR, or HI), defined as the time from the initial determination of response to the 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 the last disease assessment.

- Rate of leukemic transformation, defined as transformation at landmark time points of 6 months, 12 months, 18 months, and 24 months.

- Event-free survival (EFS), defined as the time from the first day of study drug administration (Day 1) to failure 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), defined as the time from the first day of study drug administration (Day 1) to disease recurrence or progression as defined by the 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), defined as the time from the first day of study drug administration (Day 1) to death on study. Subjects who are alive will be censored at the date of last disease evaluation.

9.3.2 Safety Analysis Endpoints

Safety endpoints will include the incidence of treatment-emergent AEs (TEAEs), characterized and graded using NCI CTCAE v4.03, and changes in laboratory results, ECG findings, physical examinations, vital signs, and ECOG performance status.

Safety will be assessed through the analysis of the reported incidence of TEAEs, including SAEs, dose-limiting toxicities, AEs leading to withdrawal, events of at least CTCAE Version 4.03 Grade 3 in severity, and AEs related to study drug. Treatment-emergent AEs are those with an onset on or after the initiation of therapy. Other safety endpoints include laboratory results, ECG findings, physical examinations, vital signs, and changes in ECOG performance status. A copy of CTCAE Version 4.03 scoring system may be downloaded from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

Adverse events will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) coding terms, system organ class, and preferred term for all subjects in the Safety population. The AEs will also be tabulated by maximum severity and relationship to study drug where applicable. Other safety endpoints, including laboratory results, vital signs, and shifts in ECG findings, will be summarized for all subjects in the Safety population. AESIs will be presented also in specific summary table(s) and listing(s).

Concomitant medications will be coded using the WHO-Drug Dictionary and they will be listed and summarized.

The rate of discontinuation, defined as the number of subjects who discontinue study drugs prior to study completion divided by the number of subjects treated, will be calculated for all subjects and for subjects who complete Cycle 3 and Cycle 6.

9.4 Independent Data Monitoring Committee

An IDMC will be set up for this study to ensure:

- protection of the subjects
- the study is conducted according to ethical standards
- the safety of the study treatments is reviewed independently during the course of the study

The IDMC will meet at intervals that it determines, for the review of data for safety trending; the IDMC will recommend continuing, modifying, or stopping the study following each review of safety data. In addition, the IDMC will advise the Sponsor whether to proceed into Stage 1b of the study.

The IDMC will have a consultative role with respect to the Sponsor and/or its representative. The Sponsor or its representative will make the final decision regarding the recommendation proposed by the committee. A separate IDMC charter will detail the activities of this committee.

10 ETHICS

This research study will be conducted according to the standards of Good Clinical Practice (GCP) outlined in the ICH E6 Tripartite Guideline, applicable government regulations, institutional research policies and procedures, and any other local applicable regulatory requirements.

10.1 Informed Consent

The patient must willingly consent after they have been informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, alternatives, side-effects, risks and discomforts. Human protection committee approval of this protocol and consent form is required. Eligible patients who wish to participate in the study will be enrolled.

Informed consent is a process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study, including the procedures to be followed, the experimental nature of the treatment, potential benefits, alternatives, side-effects, risks, and discomforts that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.

The protocol and informed consent form (ICF) will be submitted for approval to the human protection committee or equivalent that are responsible for review and approval of the study. Each ICF must include all of the relevant elements currently required by the FDA, as well as any local county authority, state regulations, and national requirements.

Before recruitment and enrollment, each prospective subject will be given a full explanation of the research study. Once the essential information has been provided, and the Investigator is

confident that the prospective subject understands the implications of participating in this research study, the prospective subject will be asked to give consent to participate in the study by signing the ICF. A notation that the subject was given a full explanation of the study, was given ample opportunity to ask questions, and a copy of the ICF which includes the subject's signature was given to the subject, must be made in the subject's medical record.

If an amendment to the protocol substantially alters the study design or the potential risks to the subjects, the subject's consent to continue participation in the study should be obtained.

10.2 Institutional Review Board (IRB)/Ethics Committee (EC)

The protocol, ICF, IB, available safety information, subject documents (e.g., study diary), subject recruitment procedures (e.g., advertisements), information about payments (i.e., Investigator payments), compensation available to the subjects, and documentation evidencing the Investigator's qualifications should be submitted to the IRB/EC for ethical review and approval prior to the study start.

The Investigator, Sponsor, and/or their designees will follow all necessary regulations to ensure appropriate, initial, and ongoing IRB/EC review. The Investigator/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB/EC for all subsequent protocol amendments and changes to the ICF.

Safety updates for pracinostat will be prepared by the Sponsor, or its representatives, as required for submission to the relevant IRB/EC.

10.3 Confidentiality

10.3.1 Subject Confidentiality

Confidentiality of subjects' personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and subsequent amendments in the US and national data protection laws. HIPAA regulations require that, in order to participate in the study, a subject must sign an authorization stating that he or she has been informed of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws
- The information collected about the research study will be kept separate from the subject's medical records, but the subject will be able to obtain the research records after the conclusion of the study

- Whether the authorization contains an expiration date
- The rights of a research subject to revoke his or her authorization.
- In the event that a subject revokes authorization to collect or use his or her PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.
- In compliance with ICH GCP guidelines, it is a requirement that the Investigator and institution permit authorized representatives of Sponsor, the regulatory authorities and the IRB/EC direct access to review the subject's original medical records at the site for verification of study-related procedures and data.
- Measures to protect confidentiality include:
  - only a unique study number will identify subjects in the CRF or other documents submitted to the Sponsor or its representative. This information will be used in the database for identification.
  - subject names or addresses will not be entered in the CRF.
  - no material bearing a subject's name will be kept on file by the Sponsor or its representative.
  - subjects will be informed of their rights within the ICF.

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Study Termination

Study termination is defined as the time when all study treatments, study related-assessments, and study data collection are completed. Upon termination of the study, the Sponsor or designee will conduct site closure activities with the Investigator or site staff (as appropriate), in accordance with applicable regulations and the study manuals and documents.

The Sponsor or designee reserves the right to temporarily suspend or terminate the study at any time for reasons including, but not limited to, safety issues or ethical reasons. The Sponsor or designee will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action, when applicable. Where required by applicable regulations, the Investigator or head of the medical institution must inform the IRB/EC.

11.2 Study Documentation and Storage

The Investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorized to make entries and/or corrections are to be

included on this document. All entries in the subject's CRF are to be supported by source documentation.

Source documents are the original documents, data, records, and certified copies of original records of clinical findings, observations and activities from which the subject's CRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The Investigator and each study staff member is responsible for maintaining a comprehensive and centralized filing system (Site Study File [SSF] or Investigator Site File [ISF]) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor (or its designees) and/or applicable regulatory authorities. The ISF/SSF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF/SSF should contain, at a minimum, all relevant documents and correspondence as outlined in ICH GCP Section 8 and Title 21 of the Code of Federal Regulations (21 CFR) Part 312.57, including key documents such as the IB, protocol, including amendments, and signed ICFs, copies of completed CRFs, IRB approval documents, Financial Disclosure forms, subject identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, and records relating to the study medication, including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain Investigator name, date drug shipped/received, date, quantity, and batch/code/ lot number. In addition, all original source documents supporting entries in the CRF must be maintained and readily available.

The Sponsor shall maintain adequate investigational product records and financial interest records as per 21CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by the FDA; or, in the event that the marketing application has not been approved by the FDA, for no less than 2 years after the last shipment/delivery of the drug for investigational use is discontinued and the FDA has been notified of the discontinuation.

The IRB/EC shall maintain adequate documentation of IRB/EC activities as per 21CFR Part 56.115 for at least 3 years after completion of the research.

The Investigator shall maintain adequate records of drug disposition, case histories, and any other study-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by the FDA; or, in the event that the marketing application has not been approved by the FDA, for no less than 2 years after the last shipment/delivery of the drug for investigational use is discontinued and the FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the Investigator additionally agrees to keep records, including the identity of all participating subjects (sufficient information to link records [e.g., CRFs, EDC records, and medical records]), all original, signed ICFs, and copies of all CRFs, EDC records, SAE

reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Sponsor or its representative will notify the Investigator(s)/institutions(s) when the study-related records are no longer required.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor or its designee should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor or its representative. The Investigator must obtain from the Sponsor or its representative written permission before disposing of any records, even if retention requirements have been met.

11.3 Data Collection

The study CRF is the primary data collection instrument for the study. All CRFs will be completed using the English language and should be kept current to enable the Sponsor or its representative to review the subjects' status throughout the course of the study.

In order to maintain confidentiality, only study number, and subject number will identify a subject in the CRF. If a subject's name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document and replaced instead with the subject number. The Investigator will maintain a personal subject identification list (subject numbers with corresponding subject identifiers) to enable records to be identified and verified as authentic.

Subject data/information will be kept confidential and will be managed according to applicable local, state, and federal regulations.

All data requested on the CRF must be supported by, and consistent with, the subject's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an 'unknown' box is not an option on the CRF, a note should be created verifying that the field was "not done" or "unknown". For any data entry error(s) made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

Once all data for that subject is final, the Investigator will sign and date the subject CRF indicating that the data in the CRF has been assessed.

11.4 Study Monitoring, Auditing, and Inspections

Participation as an Investigator in this study implies the acceptance of potential inspection by government regulatory authorities, the Sponsor, or its designee.

11.5 Quality Assurance and Quality Control

Each study site is required to have Standard Operating Procedures (SOPs) to define and ensure quality assurance/control processes for study conduct, data generation and collection, recording

of data/documentation and reporting according to the protocol, GCP, and any applicable local, national, or international regulations.

11.6 Disclosure and Publication Policy

All information provided regarding the study, as well as all information collected/documented during the course of the study, is confidential. The Sponsor or its representative reserves the right to release literature publications based on the results of the study. Results from the study will be published/presented as per the Sponsor or its representative's publication strategy. The financial disclosure information will be provided to the Sponsor or its representative prior to study participation from all Investigators and Sub-Investigators who are involved in the study and listed on Form FDA-1572.

The study will be listed on www.clinicaltrials.gov and other registries, as appropriate.

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APPENDIX A Schedule of Events

Assessments/Procedures	Screening[a]	Treatment Cycles (28 days -4 to + 7 days)[b]											End of Treatment visit[q]	Follow-up[r]
	Day -14 to 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 15[p]	Day 22[p]		
Obtain Informed Consent[c]	X													
Determine eligibility[d]	X													
Medical history, including recent smoking history	X													
Transfusion history for 8 weeks prior to first study drug administration	X	X												
Physical examination	X	X												
Vital signs[e]	X	X									X	X		
Smoking assessment[t]		X									X	X	X	
ECOG Performance Status	X	X											X	
Baseline signs and symptoms	X													
AE/toxicity assessment[f]	X	X	X	X	X	X	X[n]	X[n]	X[o]	X[o]	X	X	X	
Concomitant medication review	X	X										X	X	
12-Lead ECG in triplicate[g]	X	X												
CBC[i]	X	X									X	X	X	
Serum Chemistry[h]	X	X									X	X	X	
Serum pregnancy test (if applicable)[j]	X													
Bone marrow aspiration and biopsy[k]	X												X	
Assess study medication compliance[l]		X											X	
New Treatments and Survival														X
Dispense/administer pracinostat[l]		X												
--Azacitidine Administration (1-7)[m,n]		X	X	X	X	X	X	X						
--Azacitidine Administration (5-2-2)[m,o]		X	X	X	X	X			X	X				

Abbreviations: AE = adverse events; CBC = complete blood count; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group.

APPENDIX A Schedule of Events (Continued)

	End of Cycle 2[b]	End of Cycle 6[b]	Evidence of Disease Progression	Evidence of Hematologic CR	Prior to Transplant
Response Evaluation[s]					
CBC[i]	X	X	X	X	X
Bone marrow aspiration and biopsy[k]	X	X	X	X	X
Bone marrow aspirate and peripheral blood sample for molecular studies[k]	X	X	X	X	X

Abbreviations: CBC = complete blood count.

a Screening visit should occur ≤ 14 days before the first study treatment; the Day 1 physical examination and serum chemistry do not need to be repeated if performed within 7 days prior to Day 1.

b Study visits should occur on a 28-day schedule. A -4-day to +7-day window is allowed for each clinic visit to accommodate subject request, due to holidays, weekends, inclement weather, or other unforeseen circumstances. Treatment may also be delayed for up to 4 weeks (1 cycle) for toxicity. Treatment interruption > 4 weeks must be discussed first with the Medical Monitor.

c Written informed consent must be obtained prior to any study-required procedure being initiated.

d Inclusion/exclusion criteria must be met prior to enrollment into the study on Cycle 1 Day 1, including IPSS-R score. NOTE: IPSS in subjects enrolled under Amendment 2 should also be calculated for comparison with historical data; however, IPSS will not be used to determine eligibility (Appendix C)

e Vital signs to include height (at Screening visit only), weight, blood pressure, resting heart rate, and oral temperature.

f Monitor for AEs each visit and for 30 days after last dose of drug taken on study.

g 12-lead ECG performed in triplicate approximately once every 2 to 5 minutes to calculate the QTcF interval. On Day 1 of Cycle 1, ECGs will be obtained pre-dose, pracinostat will be taken, and azacitidine will be administered. Ninety minutes (± 15 minutes) post pracinostat dosing, triplicate ECGs will be repeated. Beyond Cycle 1, non-triplicate ECGs will be performed as clinically indicated.

h Serum chemistry: glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, calcium, carbon dioxide (CO_2), alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, total protein, albumin, and lactate dehydrogenase (LDH).

i CBC to be obtained with differential and blasts. A differential is preferred but is only required at the Screening visit and at the end of Cycles 2 and 6, with evidence of disease progression, with evidence of hematologic complete response (CR), and prior to transplant if the subject becomes a candidate for transplant. Ideally, this will be after the conclusion of ≥ 4 cycles of therapy. CBCs are to be performed at the Screening visit (two CBCs ≥ 7 days apart are required within 1 month prior to first study drug administration; the second CBC may be obtained on Cycle 1 Day 1 prior to first study drug administration), on Day 1 of each 28-day cycle, on Day 15 and Day 22 of Cycles 1 and 2 only, at response evaluations and confirmations, the End of Study visit, and with suspicion of disease progression during follow-up. CBC will consist of, at a minimum, WBC count with differential, absolute neutrophil count (ANC), lymphocyte count, red blood cell (RBC) count and indices, hemoglobin, hematocrit, platelets, and blast count where applicable.

j Serum β-hCG test for women of childbearing potential must be performed within 7 days of first study treatment; urine pregnancy tests may be performed at other visits if necessary.

APPENDIX A Schedule of Events (Continued)

k Bone marrow biopsy (BMBx) and aspirate must be performed within 28 days prior to planned first study treatment. For response assessments, BMBx and aspirate, including classic cytogenetics, FISH (fluorescence in-situ hybridization), and molecular studies* (if these tests were done at baseline), and slides will be collected. This will occur at the end of Cycles 2 and 6; with evidence of hematologic CR, which may occur after Cycle 6; at the end of study (if more than 56 days after last BM assessment); with evidence of disease progression; and prior to transplant if the subject becomes a candidate for transplant. Ideally, transplant will be after the conclusion of ≥ 4 cycles of therapy. A CBC with differential will be required for confirmation of CR or partial response (PR) 8 weeks following the initial report of response. Once a marrow CR is documented, there is no need to repeat a BMBx unless clinically indicated.

l Pracinostat capsules will be dispensed to the subject at the beginning of each cycle. The capsules are to be taken before azacitidine administration 3 times each week (e.g., Monday, Wednesday, and Friday) for 3 weeks, followed by 1 week of rest; this scheme will be repeated for every 28-day cycle. Following Cycle 1, study medication compliance will also be assessed on Day 1 of each cycle. Subjects will be administered their study medication at the clinic on Day 1 of Cycle 1 and will self-administer at home on all other days (see Section 5.2).

m Azacitidine is to be administered at 75 mg/m^2 via subcutaneous (SC) injection or intravenous (IV) infusion 7 days of every 28-day cycle at about the same time on each administration day.

n Azacitidine administration: Days 1 through 7 of every 28-day cycle.

o Azacitidine administration: Days 1 through 5, and Days 8 and 9 of every 28-day cycle. Days 6 and 7 will be rest days.

p Only Cycles 1 and 2 have a Day 15 and Day 22 visit.

q End of Study evaluations are required no less than 7 days and no more than 30 days after treatment ends (or prior to starting new treatment, if urgent treatment is required). End of Study BMBx and aspirate (including cytogenetics, FISH, and molecular studies*, if done at baseline, and slides) are required to be performed if: a subject discontinues due to disease progression without clear evidence of progression by peripheral blood counts, due to an AE, or prior to BM transplant. This is required if a BMBx and aspirate have not been obtained within 56 days prior to study discontinuation.

r After subjects discontinue study drug, they will be followed every 3 months (±1 month) until death or study termination to collect information on progression, any new treatments, and survival (e.g., date and cause of death). With suspicion of disease progression, a CBC (including 3-part differential, platelets, and blasts) may be performed (optional). Subjects may be contacted during outpatient visits or by telephone.

s A BMBx and aspirate as well as a CBC with differential will be required at the end of Cycles 2 and 6, with evidence of disease progression, with evidence of hematologic CR, and prior to transplant if the subject becomes a candidate for transplant.

t After the Cycle 3 visits, smoking assessments for subjects enrolled under Amendment 1 will only occur at the Day 1 visit of each cycle.

* FISH and molecular tests should only be performed as part of the patient's standard of care.

APPENDIX B: World Health Order (WHO) Classifications of MDS

Name	Dysplastic Lineages	Cytopenias*	Ring Sideroblasts as % of Marrow Erythroid Elements	BM and PB Blasts	Cytogenetics by Conventional Karyotype Analysis
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	< 15%/< 5%†	BM < 5%, PB < 1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1-3	< 15%/< 5%†	BM < 5%, PB < 1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)					
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	1	1 or 2	≥ 15%/≥ 5% †	BM < 5%, PB < 1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with multilineage dysplasia (MDS-RS-MLD)	2 or 3	1-3	≥ 15%/≥ 5% †	BM < 5%, PB < 1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	1-3	1-2	None or any	BM < 5%, PB < 1%, no Auer rods	del(5q) alone or with 1 additional abnormality except −7 or del(7q)
MDS with excess blasts (MDS-EB)					
MDS-EB-1	0-3	1-3	None or any	BM 5–9% or PB 2–4%, no Auer rods	Any
MDS-EB-2	0-3	1-3	None or any	BM 10–19% or PB 5–19% or Auer rods	Any
MDS, unclassifiable (MDS-U)					
with 1% blood blasts	1-3	1-3	None or any	BM < 5%, PB = 1%,‡ no Auer rods	Any
with single lineage dysplasia and pancytopenia	1	3	None or any	BM < 5%, PB < 1%, no Auer rods	Any
based on defining cytogenetic abnormality	0	1-3	< 15%§	BM < 5%, PB < 1%, no Auer rods	MDS-defining abnormality
Refractory cytopenia of childhood	1-3	1-3	None	BM < 5%, PB < 2%	Any

Abbreviations: BM = bone marrow; MDS = myelodysplastic syndrome; PB = peripheral blood.

* Cytopenias defined as: hemoglobin, < 10 g/dL; platelet count, < 100×10^9/L; and absolute neutrophil count, < 1.8×10^9/L. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. PB monocytes must be < 1×10^9/L.

† If *SF3B1* mutation is present.

‡ One percent PB blasts must be recorded on at least 2 separate occasions.

§ Cases with ≥ 15% ring sideroblasts by definition have significant erythroid dysplasia, and are classified as MDS-RS-SLD.

Reference: Vardiman 2009, Arber 2016.

APPENDIX C: Revised International Prognostic Scoring System (IPSS-R) for MDS

Note: IPSS-R scoring is not applicable to CMML-1 and CMML-2 subtypes.

Sum the scores for each feature:

Prognostic variable	Score Value						
	0	**0.5**	**1**	**1.5**	**2**	**3**	**4**
Karyotype†	Very Good	-	Good	-	Intermediate	Poor	Very Poor
Marrow blasts (%)	≤ 2	-	> 2 – < 5	-	5–10	> 10	-
Hemoglobin (g/dL)	≥ 10	-	8 – < 10	< 8	-	-	-
Platelet Count (× 10^9/L)	≥ 100	50 – < 100	< 50	-	-	-	-
Absolute Neutrophil Count (× 10^9/L)	≥ 0.8	< 0.8	-	-	-	-	-

† Very Good karyotype = -Y, del(11q);
Good karyotype = 46XX, 46XY, del(5q), del(12p), del(20q), double including del(5q);
Intermediate karyotype = del(7q), +8, +19, i(17q), any other single or double independent clones;
Poor karyotype = -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex with 3 abnormalities;
Very Poor karyotype = complex with > 3 abnormalities.

Use the summed scores to determine risk category and prognosis:

Risk Category (% IPSS-R population)	**Overall Score**	**Median Survival (years)**	**Time (years) for 25% of Patients to Progress to Acute Myeloid Leukemia**
Very Low (19)	≤ 1.5	8.8	Not reached
Low (38)	> 1.5 – 3	5.3	10.8
Intermediate (20)	> 3 – 4.5	3.0	3.2
High (13)*	> 4.5 – 6	1.6	1.4
Very High (10)*	> 6	0.8	0.73

* Required for eligibility per inclusion criterion #3. (Greenberg 2012)

International Prognostic Scoring System (IPSS) for MDS

The International Prognostic Scores (IPSS) score will not be used as an inclusion/exclusion criterion, however the IPSS will be recorded in all enrolled subjects to facilitate the comparison of IPSS scores with prior studies (Greenberg 1997).

Use the table below to determine the IPSS sum scores.

IPSS for MDS: Survival and AML Evolution

	Score Value				
Prognostic Variable	**0**	**0.5**	**1.0**	**1.5**	**2.0**
BM Blasts (%)	< 5	5 to 10	—	11 to 20	21 to 31
Karyotype[a]	Good	Intermediate	Poor		
Cytopenias[b]	0/1	2/3			

Scores for risk groups are as follows: Low, 0; INT-1, 0.5 to 1.0; INT-2, 1.5 to 2.0, and High, ≥ 2.5.
[a] Good: normal, — Y, del(5q), del(20q); Poor: complex (≥ 3 abnormalities) or chromosome 7 anomalies; Intermediate: other abnormalities.
[b] Cytopenia is defined as hemoglobin < 10 g/dL, absolute neutrophil count < 1,500/µL, and a platelet count < 100,000/µL.
Source: Greenberg 1997

APPENDIX D: International Working Group (IWG) Response Criteria and Modified IWG Response Criteria for Hematological Improvement

Proposed Modified International Working Group Response Criteria for Altering Natural History of MDS	
Category	**Response Criteria (responses must last at least 28 days)**
Complete remission	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines* Persistent dysplasia will be noted*† Peripheral blood‡ Hemoglobin ≥ 11 g/dL Platelets ≥ 100 × 10^9/L Neutrophils ≥ 1.0 × 10^9/L† Blasts 0%
Partial remission	All CR criteria if abnormal before treatment except: Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5% Cellularity and morphology not relevant
Marrow CR†	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment† Peripheral blood: if HI responses, they will be noted in addition to marrow CR†
Stable disease	Failure to achieve at least PR, but no evidence of progression for > 8 weeks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following: Return to pretreatment bone marrow blast percentage Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets Reduction in hemoglobin concentration by ≥ 1.5 g/dL or transfusion dependence
Cytogenetic response	Complete: Disappearance of the chromosomal abnormality without appearance of new ones Partial: At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with: Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts 5% – 10% blasts: ≥ 50% increase to > 10% blasts 10% – 20% blasts: ≥ 50% increase to > 20% blasts 20% – 30% blasts: ≥ 50% increase to > 30% blasts Any of the following: At least 50% decrement from maximum remission/response in granulocytes or platelets Reduction in hemoglobin by ≥ 2 g/dL Transfusion dependence
Survival	Endpoints: Overall: death from any cause Event free: failure or death from any cause PFS: disease progression or death from MDS DFS: time to relapse Cause-specific death: death related to MDS

Reference: Cheson 2006.

Abbreviations: CR = complete response; DFS = disease-free survival; FAB = French-American-British; MDS = myelodysplastic syndrome; PFS = progression-free survival; PR = partial response

Deletions to IWG response criteria are not shown. To convert hemoglobin from g/dL to g/L, multiply g/dL by 10.

* Dysplastic changes should consider the normal range of dysplastic changes (modification) (Ramos et al. 1999)

† Modification to IWG response criteria.

‡ In some circumstances, protocol therapy may require the initiation of further treatment (e.g., consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

Modified IWG Response Criteria for Hematological Improvement	
Hematological Improvement*	**Response Criteria (responses must last at least 8 weeks) †**
Erythroid response (pretreatment, < 11 g/dL) (HI-E)	Hemoglobin increase by ≥ 1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a hemoglobin of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation†
Platelet response (pretreatment, < 100×10^9/L) (HI-P)	Absolute increase of ≥ 30×10^9/L for patients starting with > 20×10^9/L platelets Increase from < 20×10^9/L to > 20×10^9/L and by at least 100%†
Neutrophil response (pretreatment, < 1.0×10^9/L) (HI-N)	At least 100% increase and an absolute increase > 0.5×10^9/L†
Progression or relapse after HI‡	At least 1 of the following: • At least 50% decrement from maximum response levels in granulocytes or platelets • Reduction in hemoglobin by ≥ 1.5 g/dL • Transfusion dependence

Abbreviations: HI = hematologic improvement; RBC = red blood cell;

Deletions to the IWG response criteria are not shown.

To convert hemoglobin levels from g/dL to g/L, multiply g/dL by 10.

* Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) ≥ 1 week apart (modification).

† Modification to IWG response criteria.

‡ In the absence of another explanation, such as acute infection, repeated courses of chemotherapy (modification), gastrointestinal bleeding, hemolysis, and so forth. It is recommended that the 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

APPENDIX E: ECOG Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Status Scale	
Score	**Description**	**Percent**	**Description**
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or do normal 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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead	0	Dead

References: Oken 1982, Karnofsky 1948.

APPENDIX F: New York Heart Association (NYHA) Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease:

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Reference: NYHA 1994.

APPENDIX G: Guidelines for Women of Childbearing Potential and Fertile Male Subjects

Acceptable Contraception Methods:

Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for 30 days after stopping treatment.

Highly effective contraception is defined as:

True Abstinence	When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
Sterilization	When a woman of childbearing potential has had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to study entry. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
Male Partner Sterilization	When the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate.
Use of a combination of any two of the following (one from a + one from b):	a) Placement of an intrauterine device (IUD) or intrauterine system (IUS) or established use of oral, injected, or implanted hormonal methods of contraception b) Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

Fertile male subjects, defined as all males physiologically capable of conceiving offspring, with female partners of childbearing potential must use condoms plus spermicidal agent during the study treatment period and for 30 days after the last dose of study drug, and should not father a child during this period.

Male subjects must also refrain from donating sperm during their participation in the study.

Unacceptable Contraception Methods:

Unacceptable contraception methods for women of childbearing potential include:

- IUD progesterone T
- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

Pregnancies

To ensure subject safety, each pregnancy in a subject on study treatment must be reported within 24 hours of learning of its occurrence: refer to the study reference manual for reporting contact information. The pregnancy should be followed up for 3 months after the termination of the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on the eCRF and reported by the Investigator. Pregnancy follow-up should be recorded and should include an assessment of the possible relationship to the study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Women Not of Childbearing Potential are defined as follows:

- Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms)
- Women who are permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy)
- Women who are > 45 years-of-age, not using hormone-replacement therapy and who have experienced total cessation of menses for at least 12 months ***or*** who have a follicle stimulating hormone (FSH) value > 40 mIU/mL and an estradiol value < 40 pg/mL (140 pmol/L)
- Women who are > 45 years-of-age, using hormone-replacement therapy and who have experienced total cessation of menses for at least 1 year ***or*** who have had documented evidence of menopause based on FSH > 40 mIU/mL and estradiol < 40 pg/mL prior to initiation of hormone-replacement therapy

APPENDIX H: Drugs that Prolong the QT Interval and/or Induce Torsades de Pointes

Drugs with a Risk of Prolonging the QT Interval and/or Torsades de Pointes

Amiodarone	Clarithromycin	Haloperidol	Procainamide
Arsenic trioxide	Disopyramide	Ibutilide	Quinidine
Asetemizole	Dofetilide	Levomethadyl	Sevoflurane
Azithromycin	Domperidone	Mesoridazine	Sotalol
Bepridil	Droperidol	Methadone	Sparfloxacin
Chloroquine	Erythromycin	Moxifloxacin	Terfenadine
Chlorpromazine	Escitalopram	Pentamidine	Thioridazine
Cispride	Flecainide	Pimozide	Vandetanib
Citalopram	Halofantrine	Probucol	

Drugs with a Possible Risk of Prolonging the QT Interval and/or Torsades de Pointes

Alfuzosin	Gatifloxacin	Ofloxacin	Saquinavir
Artenimol+piperaquine	Gemifloxacin	Olanzapine	Sertindole
Atazanavir Bedaquiline	Granisetron	Ondansetron	Sunitinib
Clozapine	Iloperidone	Oxytocin	Tacrolimus
Dolasetron	Indapamide	Paliperidone	Tamoxifen
Dronedarone	Isradipine	Pasireotide	Telithromycin
Eribulin	Lapatinib	Perflutren	Tizanidine
Famotidine	Levofloxacin	Lipid	Tolterodine
Felbamate	Lithium	Microspheres	Vardenafil
Fingolimod	Mirtazapine	Promethazine	Venlafaxine
Foscarnet	Moexipril/HCTZ	Quetipine	Voriconazole
Fosphenytoin	Nicardipine	Ranolazine	Ziprasidone
	Nilotnib	Risperidone	
		Roxithromycin	

Drugs with a Conditional Risk of Prolonging the QT Interval and/or Torsades de Pointes (Should be used with Investigator discretion)

Amantadine	Diphenhydramine	Itraconazole	Ritonavir
Amisulpride	Doxepin	Ketoconazole	Sertraline
Amitriptyline	Fluconazole	Nortriptyline	Solifenacin
Chloral Hydrate	Fluoxetine	Paroxetine	Trazodone
Ciprofoxacin	Galantamine	Protriptyline	Trimethoprim-Sulfa
Clomipramine	Imipramine	Quinine	Trimipramine
Desipramine		Sulfate	

The following website was used as a guide for drugs which may prolong the QT interval: https://www.crediblemeds.org. Medications listed on the website which do not appear in this appendix may be used at the discretion of the Investigator.

APPENDIX I: Substrates of CYP1A2, CYP2B6 and CYP3A4

For the complete list please refer to source: FDA website - Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers (Sep 26th, 2016).

Examples of CYP1A2 substrates

	Sensitive substrates	Moderate sensitive substrates
CYP1A2	alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon, theophylline, tizanidine	clozapine, pirfenidone, ramosetron

Examples of CYP2B6 substrates

	Sensitive substrates	Moderate sensitive substrates
CYP2B6	bupropion	efavirenz

Examples of CYP3A4 substrates

	Sensitive substrates	Moderate sensitive substrates
CYP3A4	alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil, budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan	alprazolam, aprepitant, atorvastatin, colchicine, eliglustat, pimozide, rilpivirine, rivaroxaban, tadalafil