SGI-110-04

Statistical Analysis Plan

A Phase 3, Multicenter, Open-Label, Randomized Study of SGI-110 Versus Treatment Choice (TC) in Adults With Previously Untreated Acute Myeloid Leukemia (AML) Who Are Not Considered Candidates for Intensive Remission Induction Chemotherapy

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ABBREVIATIONS AND DEFINITIONS

AE	adverse event
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
BDM	Biostatistics and Data Management
BID	twice daily
BM	bone marrow
BSA	body surface area
CI	confidence interval
C_{max}	maximum concentration
CR	complete response
CRc	composite CR (CRc = CR + CRp + CRi)
CRi	CR with incomplete blood count recovery
CRO	contract research organization (CRO)
CRp	CR with incomplete platelet recovery
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EQ VAS	EQ visual analogue scale
FAB	French-American-British
HCT	hematopoietic cell transplant
HR	hazard ratio
ITT	intent-to-treat
IWG	International Working Group
LDAC	low-dose Ara-C
MDS	myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
NCCN	National Comprehensive Cancer Network
NDAOH	number of days alive and out of the hospital
NE	nonevaluable
NR	nonresponders
OR	odds ratio
OS	overall survival
PB	peripheral blood
PD	pharmacodynamic(s)
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PT	preferred term
QOL	quality of life
QTc	heart rate corrected QT interval
ROW	rest of world
Remission	equivalent to "response"
Response	equivalent to "remission"
RR	relative risk
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SGI-110	guadecitabine
SOC	system organ class
TC	treatment choice

1.0 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on SGI-110-04 protocol version 2, dated 6 March 2015. Analyses and statistical reporting for SGI-110-04 will be conducted by Astex Pharmaceuticals Biostatistics department with the interim analysis results as reported by the study's Data Monitoring Committee (DMC).

1.1 Acute Myeloid Leukemia in Patients Who Are Not Considered Candidates for Intensive Remission Induction Therapy and the Elderly

Acute myeloid leukemia (AML) is a genetically heterogeneous group of cancers that have in common clonal proliferation and arrested differentiation of myeloid precursors. Incidence increases with age and is about 12 cases per 100,000 for those at and above the median age at diagnosis of 65 years (Schiffer and Anastasi 2014). Overall 5-year survival is 15% and varies substantially with age (Shah et al 2013). Patients age 70-79 years and over age 79 years have 5 year survival rates of 3% and 0%, respectively.

In addition to age, other adverse prognostic indicators in AML include poor performance status, adverse cytogenetic or molecular genetic findings, past exposure to cytotoxic or radiation therapy, and history of myelodysplasia or another hematologic disorder (Schiffer 2014). There is a correlation between age at diagnosis of AML and complex cytogenetic disease characteristics. Complex karyotype also correlates with disease resistance to therapy (Grimwade et al 2001). In summary, AML in patients who are not considered candidates for intensive remission induction chemotherapy, particularly elderly patients, remains a persistent unmet medical need.

1.2 Treatment Options for Patients with AML Who Are Not Considered Candidates for Intensive Remission Induction Therapy

No standard therapy exists for patients with previously untreated AML who are not candidates for intensive remission induction chemotherapy. The National Comprehensive Cancer Network (NCCN), European Leukemia Net, and European Society for Medical Oncology all recommend possible treatments with low-dose Ara-C (LDAC), azacitidine, or decitabine in addition to enrolling patients in experimental treatment clinical trials.

In Study SGI-110-04, treatment choice (TC) will be compared with guadecitabine (SGI-110). Available TCs will depend on which TCs are approved locally. TC includes cytarabine, decitabine, or azacitidine.

1.3 Guadecitabine

Guadecitabine is a dinucleotide of decitabine and deoxyguanosine, designed to protect the active decitabine moiety from inactivation by cytidine deaminase (Griffiths et al 2013).

Rationale for Study SGI-110-04 comes from guadecitabine's molecular structure, pharmacokinetic (PK), pharmacodynamic (PD), and clinical data. Human PK data confirms that

gradual in vivo dinucleotide cleavage increases decitabine exposure time and effective half-life relative to decitabine IV infusion. Prolonged exposure time is predicted to increase efficacy because decitabine activity is dependent on its incorporation into DNA during DNA synthesis, ie, S-phase of the cell cycle (Griffiths et al 2013; Karahoca and Momparler 2013). Prolonged exposure results in more cancer cells susceptible to decitabine activity as they enter into S-phase. Also, a lower decitabine C_{max} after guadecitabine relative to decitabine IV infusion might improve safety for toxicities associated with peak decitabine concentrations.

During the first-in-human Phase 1 SGI-110-01 Dose Escalation, potent DNA demethylation, complete response (CR) and other clinical responses were observed in heavily pretreated subjects with AML and MDS (myelodysplastic syndromes) (Issa et al 2015), including those previously treated with other existing hypomethylating agents (decitabine and azacitidine).

In the Phase 2 SGI-110-01 Dose Expansion, 51 elderly subjects with AML who had other poor prognostic features and were not eligible for intensive chemotherapy received guadecitabine. The CR rate of 37% and composite CR (CRc) rate of 57% (Kantarjian et al 2015) exceeded those observed for available therapies in randomized, multicenter studies (CR rates of 8% to 20% and CRc rates of 11% to 28%) (Kantarjian et al 2012; Dombret et al 2014; Burnett et al 2007).

2.0 STUDY OBJECTIVES

2.1 Primary Objective

To assess and compare efficacy (CR rate and overall survival [OS]) between guadecitabine and TC in adults with previously untreated AML who are not considered candidates for intensive remission induction chemotherapy.

2.2 Secondary Objectives

To assess and compare effects of guadecitabine and TC in adults with previously untreated AML who are not considered candidates for intensive remission induction chemotherapy with respect to the following variables:

- CRc (CR + CR with incomplete blood count recovery [Cri] + CR with incomplete platelet recovery [CRp]) rate.
- Number of days alive and out of the hospital (NDAOH).
- Progression-free survival (PFS).
- Transfusion needs.
- Health-related quality of life (QOL).
- Duration of CR.
- Safety.

2.3 Exploratory Objectives

- [redacted]
- [redacted]

3.0 STUDY DESIGN

3.1 Overall Study Design

This is a phase 3, multicenter, randomized, open-label study of guadecitabine versus TC. Blinded central reading of marrow and disease response will be performed. Subjects will be adults with previously untreated AML who are unfit to receive and not candidates for intensive remission induction chemotherapy.

Approximately 800 subjects from approximately 100-160 study centers will be randomly assigned (1:1) to 1 of 2 groups:

- Guadecitabine: 60 mg/m^2 guadecitabine given SC daily for 5 days (Days 1-5, Daily×5) in 28-day cycles.
- TC: subjects will be assigned (before randomization) by the investigator to 1 of the following treatment regimens:
  - 20 mg cytarabine (Ara-C) given SC BID on Days 1-10 every 28 days.
  - 20 mg/m^2 decitabine (Dacogen) given IV on Days 1-5 every 28 days.
  - 75 mg/m^2 azacitidine (Vidaza) given IV or SC on Days 1-7 every 28 days.

The randomization will have a ratio of 1:1 between guadecitabine and TC groups, and will be stratified by age (<75 or ≥75 years old), ECOG performance status (0-1, 2-3), study center region (North America, Europe, rest of world [ROW]), and secondary AML or poor-risk cytogenetics (Yes, No/Unknown). Subjects who are older (≥75 years) or have a poor performance status (2 or 3) tend to have worse response and survival than younger (<75 years) subjects or subjects with a good performance status (0 or 1). Similarly, subjects with a secondary AML or poor-risk cytogenetics generally do not respond to treatment well and have a shorter survival time. In addition, prognosis could have regional differences due to multiple factors including variable levels of Standard of Care. Stratification by these known and important prognostic factors measured at baseline prevents imbalance between treatment groups within strata, and could reduce bias and improve power of the study.

Selection of 1 of the TCs must be made prior to the randomization of each subject. Subjects should receive study treatment as soon as possible after randomization (maximum of 1 week between randomization and treatment).

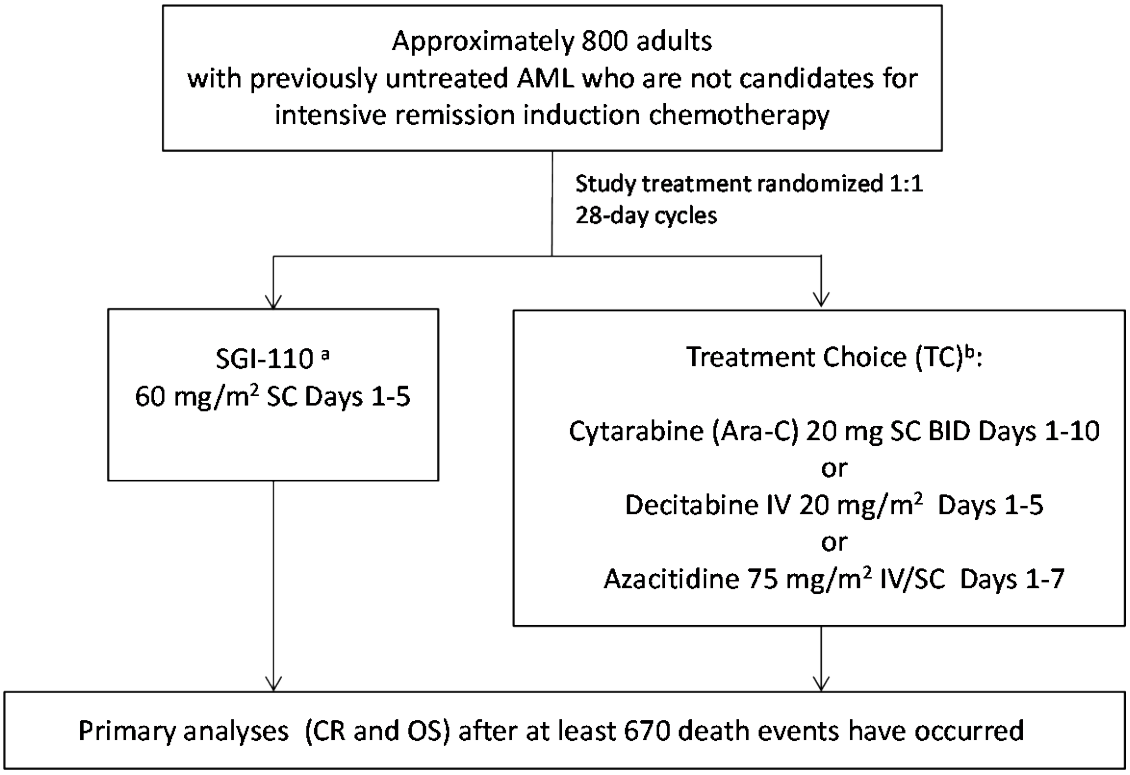
The sponsor, investigators and study subjects are not blinded in this study. However, to minimize the potential bias associated with assessment of treatment outcome, response will be determined

by a blinded independent central response reviewer, based on assessment by a blinded independent central pathologist. Refer to Section 11.6 of the study protocol. The specific process used for handling test samples and reports will be described separately.

Peripheral blood (PB) will be assessed at baseline and on Day 1 of each cycle for response status evaluation. Bone marrow (BM) aspirate/biopsy will be performed at screening and then at the end of Cycles 2, 4, and 6 unless PB shows persistence of leukemic blasts that excludes the possibility of a marrow response. After Cycle 6 BM assessment, BM aspirate/biopsy will be repeated every 3 months for the first year on study and then every 6 months thereafter until PB or BM assessment shows disease progression or relapse. Response evaluation will be based on BM blinded assessment and the most concomitant PB counts. After blinded BM response is confirmed, assessment of normal count recovery will be done based initially on the most concomitant PB and in later cycles on PB counts from Day 1 of each cycle to avoid transient treatment-induced normal count suppression.

Figure 1 below summarizes the study design.

Figure 1: Study Schema



[a] Treatment with guadecitabine should continue for at least 6 cycles in the absence of unacceptable toxicity or AML progression requiring alternative therapy. Beyond 6 cycles, treatment should continue as long as the subject continues to benefit based on investigator judgment.

[b] TC will be determined before randomization and treatment with the regimens described in the study protocol (Section 7.2) should be used. Other treatment parameters should be applied according to institutional standard practice and approved local prescribing information.

The study is expected to enroll the required number of subjects in 21 months with an additional follow-up of 12-15 months before the planned primary analysis. The expected duration of the study from the first subject enrollment to the planned primary analysis is approximately 3 years.

3.2 Study Endpoints

3.2.1 Co-primary Endpoint

- CR rate based on modified International Working Group (IWG) 2003 AML Response Criteria.
- OS, defined as the number of days from randomization to death.

3.2.2 Secondary Endpoints

- CRc (CR+CRi+CRp) rate.
- NDAOH.
- PFS, defined as the number of days from date of randomization to date of disease progression, initiation of an alternative anti-leukemia therapy, or death, whichever occurs first.
- Number of red blood cell (RBC) or platelet transfusions (units) over the duration of the study treatment.
- Health-related QOL by EQ-5D (consisting of the EQ-5D-5L descriptive system and the EQ Visual Analogue Scale [EQ VAS]).
- Duration of CR, defined as the time from first CR to time of relapse.
- Incidence and severity of adverse events (AEs).
- 30- and 60-day all-cause mortality.

4.0 SAMPLE SIZE

By trial design, the overall (2-sided) alpha level of 0.05 is split between the co-primary endpoints of CR (0.04) and OS (0.01). A formal interim analysis will be performed only for OS using a group sequential boundary preserving an overall (2-sided) 0.01 alpha level. The sample size calculation for the primary analysis of CR is based on testing at the 0.04 nominal alpha level. If statistical significance is achieved for CR, hierarchically, the final analysis of OS will be conducted to preserve an overall 2-sided 0.05 alpha level, accounting for alpha spent at the interim analysis of OS, as described in Section 11.6.7 and Section 11.9 of the study protocol (see Section 7.3.7 and 7.6). The sample size calculation for OS will be shown for the setting of a 2-sided 0.05 alpha level.

Assuming a CR rate of approximately 0.20 (Kantarjian et al 2012; Fenaux et al 2010; Burnett et al 2007) for subjects treated in the TC group (all TC therapies combined) and assuming an increase in CR rate to 0.30 or higher can be achieved by treating subjects with guadecitabine,

800 subjects (400 per treatment group) will provide approximately 89% power to detect the overall difference of 0.10 when using a 2-sided Cochran Mantel-Haenszel test having 2-sided alpha level of 0.04. For the purpose of this sample size calculation, the constant CR rates of 0.20 and 0.30 for the TC and guadecitabine groups, respectively, are assumed for each stratum.

For survival, an analysis at 670 death events will provide 90% power to detect a HR of approximately 0.78 (a difference in median survival of 7 months in the TC group versus 9 months in the guadecitabine group), when using a 2-sided stratified log-rank test at an 0.05 alpha level. Accrual is expected to be uniform over a 21 month enrollment period, with an additional follow-up of 12 months. Hence, the assessment of survival needs approximately the same sample size of 800 subjects. Primary response and survival analyses will be performed after 670 death events have occurred. For the purpose of this sample size calculation, a constant HR of approximately 0.78 was assumed for all strata defined by the stratification factors.

5.0 ANALYSIS SETS

5.1 All Subject Analysis Set

This analysis set will contain information of all screened subjects, including those who did not meet the study entry criteria or did not receive a study treatment.

5.2 Efficacy Analysis Set

Efficacy analyses will be based on intent-to-treat (ITT) principle. The Efficacy Analysis Set will include data from all subjects randomly assigned to study treatment. All data will be included and no subjects excluded because of protocol violations. For the analysis of efficacy data, subjects will be included in the treatment group according to their randomly assigned treatment.

For NDAOH, transfusions, and health-related QOL by EQ-5D-5L, the primary analysis will include only the data collected during the first 6 months of the study because, during this study period, subjects are assessed whether or not they are still on study treatment. Secondary analysis may also include data beyond the first 6 months of the study (eg, over the entire period of study treatment).

5.3 Safety Analysis Set

The Safety Analysis Set will include data from all subjects randomly assigned to study treatment who receive any amount of study treatment or any component of a multi-dose study treatment regimen. All data will be included and no subjects excluded because of protocol violations. For safety data analysis, subjects will be included in the treatment group according to the treatment they actually receive. If more than one type of study treatment was given for any subject during the study, the initial treatment received by the subject will be used to determine which treatment group and which specific TC treatment the subject belongs to.

5.4 PK Analysis Set

The PK Analysis Set will include all available plasma concentrations and PK parameters for guadecitabine and decitabine from subjects at selected centers who have received guadecitabine or decitabine IV and for whom PK samples were collected and successfully analyzed. PK data will be analyzed using the PK Analysis Set.

5.5 PD Analysis Set

Pharmacodynamics analyses are not applicable to this study.

6.0 SCHEDULE OF ANALYSES

Data listings and summary tables will be reviewed by the DMC approximately every 6 months to ensure the safety of study subjects and to enhance the quality of trial conduct (refer to protocol Section 4.4 and the DMC Charter). These data listings and summary tables will be generated by Axio Research LLC, an independent contract research organization (CRO) supporting the DMC activities.

An interim analysis of OS will also be conducted by the DMC when approximately half of the required death events have occurred. All available study data will be analyzed after 670 death events have occurred to achieve a mature analysis of OS.

7.0 STATISTICAL ANALYSIS

Unless otherwise specified, all statistical tests and confidence intervals (CIs) created will be two-sided with alpha = 0.05 (see Section 7.3.7). The SAS® statistical package (SAS Institute Inc., Cary, NC, USA, version 9.3 or a later version) will be used for the analyses.

The following data listings by study center and subject will be provided, as recommended by the ICH E3 guideline "Structure and Content of Clinical Study Reports": discontinued subjects, important protocol deviations, demographics, compliance and/or drug concentration data (including specific batch number), individual efficacy response data, subjects excluded from the efficacy analysis, AEs, medications, and the protocol specified laboratory measurements. Additional data listings may be generated to support other relevant discussions in CSR.

Summary tables of disposition, baseline, dosing, efficacy, safety, and PK data will be provided, by treatment group (guadecitabine or TC). In addition, similar tables will be generated, as appropriate, comparing guadecitabine to each TC option in the patients randomized under that preselected TC option.

7.1 Subject Disposition

Subject disposition including numbers screened, randomized, treated, and treatment discontinuation by reason, as well as the reasons for withdrawal from study will be summarized using frequencies and percentages based on information collected on the relevant study case

report form pages. Sample size for efficacy and safety analysis sets will be clearly identified. All Subject Analysis Set will be used for the disposition analysis.

7.2 Demographic and Other Baseline Characteristics

The demographic variables consist of age, age category, sex, ethnicity, race and geographical region. Baseline characteristics include height, weight, body surface area (BSA), ECOG performance status, AML category by French-American-British (FAB) classification as well as by WHO classification, time since AML diagnosis, whether the AML is secondary to MDS or other antecedent hematologic disorder, cytogenetic risk levels, peripheral blood counts of hemoglobin, platelets, total white blood cells (WBCs) with blasts counts, BM blasts and presence of baseline genetic mutations in several genes including but not limited to FLT3-ITD, NPM1, and CEBPA. Other baseline variables such as relevant medical history or other medically relevant criteria could also be included in the baseline tables.

Baseline values are generally the values collected right before randomization during the screening period. For analysis purposes, the value collected closest to but before randomization will be used as the baseline value for a particular variable. For variables which are collected on Day 1 of Cycle 1 (C1D1) but not during the screening period, the C1D1 values will be used as the baseline values.

Age at baseline, if not already provided through data collection, will be calculated as the integer part of (date of consent - date of birth)/365.25.

Time since diagnosis will be calculated as the (date of randomization - date of diagnosis). If the day is missing for date of diagnosis, the 15th of the month is used. If the month is missing, July 1st is used. If the year is missing, the date is left as missing. Additional date imputation details are contained in the Astex Data Programming Conventions.

Subject demographic and baseline characteristics will be summarized by mean, standard deviation, median, minimum, and maximum for continuous variables; and by counts and percentages for categorical variables. Both the Efficacy and Safety Analysis Sets will be used for the summaries.

7.3 Efficacy Variables and Analyses

Efficacy analyses will be based on the Efficacy Analysis Set, except where it is specified otherwise. This section describes the analyses conducted at the primary analysis time point when 670 death events have occurred, assuming that the study continued after the planned interim analysis. The alpha levels referenced in this section are nominal alpha levels for judging statistical significance, taking into consideration the planned interim analysis and the hierarchical testing order of the (final) primary analysis. The overall experimental alpha error is controlled at the 2-sided 0.05 level.

The co-primary efficacy endpoints are CR rate based on IWG 2003 AML Response Criteria (Cheson et al 2003) and OS. If either of the co-primary efficacy endpoints reaches statistical

significance in favor of guadecitabine at either the interim analysis (OS only) or final analysis (CR and OS), then the study will be considered positive in efficacy.

Secondary efficacy endpoints include CRc, NDAOH, PFS, number of RBC transfusions, and separately, number of platelet transfusions over the duration of the study treatment, the EQ-5D-5L descriptive system and the EQ VAS, as well as duration of CR.

7.3.1 Criteria for Response Assessment

Modified IWG 2003 Response Criteria (Table 1) will be used by an independent blinded central reader to identify AML subjects with CR, CRp, CRi, or partial response (PR) for further statistical analyses.

Table 1: Modified 2003 IWG AML Response Criteria

Response[a]	Peripheral Blood (PB)	Bone Marrow (BM)
CR	ANC ≥1000/µL, Platelets ≥100,000/µL, independence from RBC and platelet transfusions over the past week, no leukemic blasts[b]	<5% leukemic blasts
CRp	ANC ≥1000/µL, Platelets <100,000/µL, independence from RBC transfusions over the past week, no leukemic blasts[b]	<5% leukemic blasts
CRi	ANC <1000/µL, no leukemic blasts[b]	<5% leukemic blasts
PR	ANC ≥1000/µL, Platelets ≥100,000/µL, no leukemic blasts[b]	Decrease of ≥50% in leukemic blasts to level of 5% to 25%

[a] Responses are based on both PB and BM conditions.
[b] For the purpose of response assessment and according to published IWG criteria, blasts may be seen in PB as rare PB blasts may be identified during regeneration, but the subject is in CR if BM blasts are <5% with no Auer rods (Cheson et al 2003).

ANC=absolute neutrophil count; CR=complete response; CRp=complete response with incomplete platelet recovery; CRi=CR with incomplete blood count recovery; PR=partial response.
Source: Cheson et al 2003

Subjects with these different response categories, as well as nonresponders (NR) and nonevaluable (NE) subjects will be listed and summarized using frequency counts and proportion of subjects with each category of best response. Subjects who did not have a valid post-treatment efficacy assessment (ie, no post-treatment BM/PB sample or the quality of BM/PB sample is not adequate for the central pathologist to provide an assessment of efficacy) will be classified as NE for response classifications. These subjects will be included in the denominator of the ITT analysis for calculation of different response rates. Subjects who cannot be classified into a response category (CR, CRp, CRi, PR) or the NE category will be classified as NR.

In particular, the best response in the order of CR, CRp, CRi and PR will be used when a subject experienced different response levels at different visits. Subjects who progressed (see Section 7.3.6 for definition) without first having a response (CR, CRp, CRi, or PR) will be included in the NR category for summary purpose.

Response rate based on the central reader's assessments will be calculated for the best response categories described below to assess overall efficacy observed.

- CR, CRp, CRi, PR.
- Composite CR (CRc=CR+CRp+CRi).

Investigators will also provide the assessment of response using the same Modified IWG 2003 Response Criteria (Table 1). However, their assessments will only be provided in a data listing.

7.3.2 Complete Response

The primary endpoint of CR rate will be calculated as the number of subjects with a best response of CR divided by the total number of subjects included in the efficacy analysis. The CR rate will be compared between the 2 treatment groups using a Cochran Mantel-Haenszel test at an alpha level of 0.04 stratified by the stratification factors used at randomization: age (<75 or ≥75 years), ECOG performance status (0-1, 2-3), study center region (North America, Europe, ROW), and secondary AML (secondary to MDS or other antecedent hematologic disorder) or poor-risk cytogenetics (Yes, No/Unknown). The null and alternative hypotheses are:

- **Null hypothesis H_0:** CR rates are the same between the guadecitabine treatment and TC treatment
- **Alternative hypothesis H_1:** CR rates are different between the two treatment arms

A 2-sided *p* value of ≤0.04 will be judged as statistically significant. In addition, a normal approximated, two-sided 96% CI for the (Mantel-Haenszel weighted) difference in CR rates between guadecitabine treatment and TC treatment will be provided (Koch et al 1990).

The following sensitivity analyses will be conducted for the co-primary endpoint of CR rate for evaluating robustness of the treatment effect:

1) The CR rate will be compared between the guadecitabine and TC using a regular Chi-square test without stratification.
2) A logistic regression analysis will be performed for the primary endpoint of CR with treatment group (guadecitabine or TC), age (<75 or ≥75 years old), ECOG performance status (0-1, 2-3), the geographic region (North America, Europe, ROW) of the study centers, and secondary AML or poor-risk cytogenetics (Yes, No/Unknown) as fixed factors. The point estimate and 95% CI, as well as the *p* value will be provided for the odds ratio (OR) comparing the odds of being a responder in guadecitabine treatment with the odds of being a responder in TC treatment.
3) An "as-treated" analysis will be conducted on the CR rate, based on treatment actually received as described in Section 5.3, using the same Cochran Mantel-Haenszel test and same

stratification variables described above. Subjects who were randomized but not treated will not be included in this analysis.

4) The CR rate will be calculated and analyzed using the same Cochran Mantel-Haenszel test and same stratification variables described above with the subjects who were classified as nonevaluable for efficacy (NE subjects) excluded from the Efficacy Analysis Set.

5) The CR rate will be calculated and analyzed using the same Cochran Mantel-Haenszel test and stratification variables described above excluding subjects whose AML diagnosis cannot be confirmed by WHO classification by the independent central reader.

7.3.3 Overall Survival

For the OS analysis, survival time is defined as the number of days from the day the subject was randomly assigned to study treatment to the date of death (regardless of cause).

Survival time in days = (earliest date of death or censoring - date of randomization)

Survival time will be censored on the last date the subject is known alive with no event of death. OS curves will be estimated using Kaplan-Meier method and formally compared between the two treatment groups using a 2-sided stratified log-rank test, stratified by the same stratification factors used at randomization. The null and alternative hypotheses are:

- **Null hypothesis H_0:** Survival curves are the same between the two treatment arms
- **Alternative hypothesis H_1:** Survival curves are different between the two treatment arms

If the CR rate analysis is significant, OS will be tested at an alpha level of 0.05; without a significant CR rate test result, OS will be tested at an alpha level of 0.01, as described in Section 7.3.7. The stratification variables will include age (<75 or ≥75 years), ECOG performance status (0-1, 2-3), study center region (North America, Europe, ROW), and secondary AML or poor-risk cytogenetics (Yes, No/Unknown). The median (and quartiles) duration of OS and the associated 95% CI for each treatment arm will be estimated using the Kaplan-Meier method and the log(-log(.)) transformation for the survival function. The 12-month survival rate estimate will also be provided for each treatment arm.

In addition, the HR and its 95% CI will be estimated using a Cox proportional-hazard model with treatment group as the independent variable and stratified by the same randomization stratification factors as used for the log-rank test. In a supportive analysis, the assumption of proportional hazards will be evaluated to assist interpretation of the Cox regression analysis results.

The following sensitivity analyses will be conducted for the co-primary endpoint of OS for evaluating robustness of the treatment effect:

1) The OS will be analyzed using Kaplan-Meier method and compared between the guadecitabine and TC using log-rank test without stratification.
2) An "as-treated" analysis will be conducted for the OS, based on treatment actually received as described in Section 5.3, using the same Kaplan-Meier method and 2-sided stratified log-rank test described above. Subjects who were randomized but not treated will not be included in this analysis.
3) This analysis will be conducted using the same Kaplan-Meier method and 2-sided stratified log-rank test described above. However, the survival time will also be censored on the date the subject receives other anti-leukemia treatments, including chemotherapy and hematopoietic cell transplant (HCT), recognizing the fact that this analysis could diminish a true treatment effect since HCT are given to subjects whose disease is well controlled and other anti-leukemia therapies are usually given to subjects at the time of their disease progression.
4) This analysis will be conducted using the same Kaplan-Meier method and 2-sided stratified log-rank test described above, excluding subjects whose AML diagnosis cannot be confirmed by WHO classification by the independent central reader.

7.3.4 Composite CR

The CRc rate is calculated as the number of subjects with a best response of CR, CRp, or CRi divided by the total number of subjects included in the efficacy analysis. The CRc rate will be compared between the 2 treatment groups using a Cochran Mantel-Haenszel test with the stratification variables the same as for CR and OS. If CR rate analysis and OS analysis are both significant, the CRc rate will be tested at an alpha level of 0.05; with a nonsignificant CR rate result ($p>0.04$) and a significant OS result at the 0.01 level, the CRc rate will be tested at an alpha level of 0.01 (see Section 7.3.7). In addition, the 2-sided 95% (or 99%, as appropriate) CI for the Mantel-Haenszel weighted difference in CRc rate between the 2 treatment groups will be provided.

7.3.5 Number of Days Alive and Out of the Hospital

The date of each hospital admission and discharge will be collected for each subject for a minimum 6 months (and until termination of study treatment if the study treatment lasts for more than 6 months), unless the subject dies or withdraws consent prior. The duration of each hospital stay in days (regardless of the reason for hospitalization) is calculated as:

Duration = date of discharge - date of admission

For a subject who is admitted and discharged on the same day the duration of hospital stay will be 0. The total duration of all hospital stays in the first 6 months is the sum of all individual

durations of hospital stays occurred between C1D1 and Day 180. For ease of calculation, one month is defined as 30 days for analyses conducted in this study. The NDAOH within the first 6 month period is calculated as:

NDAOH = 180 - total duration of all hospital stays - number of death days before Day 180

The number of death days before Day 180 = (date of Day 180 - date of death, if death occurs before Day 180). For subjects who die on or after Day 180 the number of death days before Day 180 will be set to 0. For subjects who are lost to follow-up within 6 months (expected to be a very small number), the NDAOH will be calculated conservatively assuming that the subject would have died the day after the last contact day.

The NDAOH will be summarized by treatment group and compared between the 2 treatment groups using an analysis of variance model at an alpha level of 0.05 or 0.01 as appropriate, if the CRc test result is significant at that required level (see Section 7.3.7). The variables used for stratification at randomization will be included in the analysis of variance model as fixed factors.

In addition, to utilize the information on hospital stays beyond 6 months, the NDAOH will also be calculated in a similar way to 6 months or the date of treatment discontinuation (whichever occurs later) and summarized as a per patient-year rate for each treatment group.

7.3.6 Progression-free Survival

Progression is defined as the earliest occurrence of one of the following:

- For subjects with CR, CRi, or CRp, the confirmed (at least 2 PB samples at least 1 week apart) appearance of leukemic blasts in PB by investigator or central assessment, OR ≥5% leukemic blasts in the BM by blinded central pathologist assessment.
- For all other subjects, when PB or BM shows evidence of continued increase in blasts % that necessitates alternative therapy.
- Death.

PFS is defined as the number of days from randomization to the earliest date of investigator's assessment of disease progression, subject receives an alternative anti-leukemia therapy, or relapse by PB assessment or blinded BM assessment, whichever occurs first, or death (regardless of cause). PFS time will be censored on the last date the subject is known to be alive without a relapse/disease progression.

PFS in days = (earliest date of progression, relapse, alternative anti-leukemia therapy, death or censoring - date of randomization)

PFS will be compared between the 2 treatment groups using a stratified log-rank test (by the same stratification factors as used at randomization) at an alpha level of 0.05, or 0.01, as appropriate, if CRc and NDAOH test results are significant at that required level (see

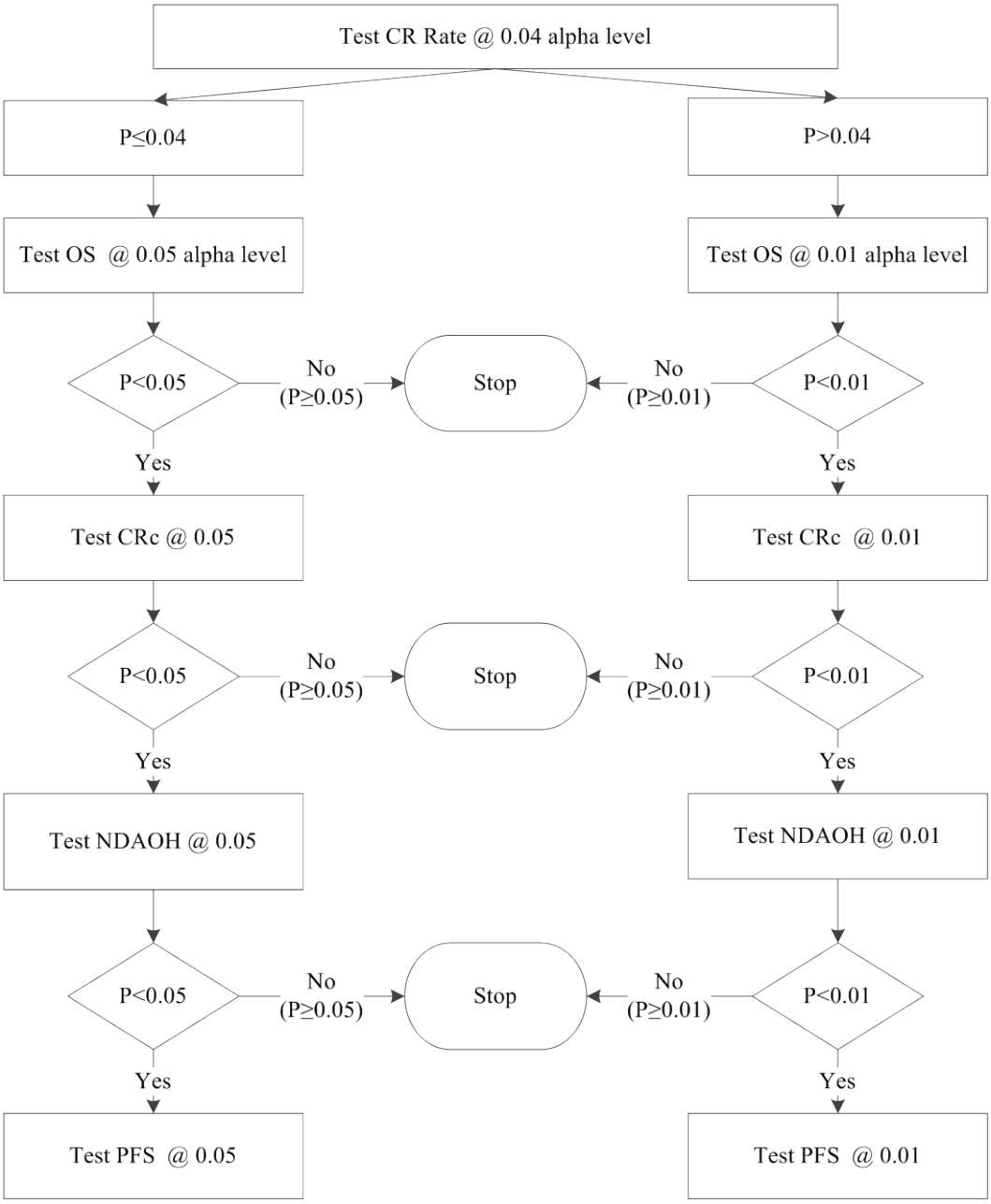
Section 7.3.7). The median (and quartiles) duration of PFS and the associated 95% CI for each treatment arm will be estimated using the Kaplan-Meier method. In addition, the HR and its 95% CI will be estimated using a Cox proportional-hazard model with treatment group as the independent variable and stratified by the same randomization stratification factors as used for the log-rank test. In a supportive analysis, the assumption of proportional hazards will be evaluated to assist interpretation of the Cox regression analysis results.

7.3.7 Test Sequence and Procedures of Statistical Tests for Efficacy Endpoints

To control the alpha errors associated with testing the multiple endpoints of CR rate, OS, CRc rate, NDAOH, and PFS, the following test sequence and procedures will be followed, assuming that the study continues after the planned interim analysis.

The primary efficacy variable CR rate will be tested first in the sequence at an alpha level of 0.04. A positive CR analysis ($p \leq 0.04$) serves as a gatekeeper (Westfall and Krishen 2001) for the subsequent analyses. If the test for CR is positive (ie, $p \leq 0.04$), then hierarchical analyses will be conducted at the 0.05 alpha level for the efficacy variables OS, CRc rate, NDAOH, and PFS (in that order). If the test for CR is not significant at the 0.04 level, then hierarchical analyses will be conducted at the 0.01 level for the efficacy variables OS, CRc, NDAOH, and PFS. The hierarchical test order and alpha value to be used for each test at the primary analysis time point are further described in Figure 2.

Figure 2: The Hierarchical Test Order and Related Alpha Values



The overall alpha error rate is controlled at the 0.05 level by following the above testing sequence and procedures.

Other secondary efficacy endpoints (number of transfusions, health-related QOL, and duration of CR) will be used as supportive evidence of the beneficial treatment effect, without formal hypothesis testing. Point estimates and 95% CIs will be obtained for the effect of treatment on these endpoints.

7.3.8 Number of RBC or Platelet Transfusions (Units)

One RBC transfusion is defined as 1 unit of RBC transfusion. Similarly, one platelet transfusion is defined as 1 unit of platelet transfusion. Dates and the number of RBC or platelet transfusions will be collected for each subject for a minimum 6 months (and until termination of study treatment if the study treatment lasts for more than 6 months), unless the subject dies or withdraws consent prior.

The total number of RBC or, separately, the total number of platelet transfusions up to the 6-month time point for each subject is counted from the date of randomization to Day 180, the date of last contact, or date of death, whichever occurs earlier. The number of transfusions up to Day 180 will be summarized using mean, standard deviation, median and quartiles. The 95% CI of the means will also be provided.

7.3.9 EQ-5D-5L Descriptive System Total Score and the EQ VAS

The EQ-5D-5L descriptive system scores and the EQ VAS will be collected for each subject for a minimum 6 months unless the subject dies or withdraws consent prior. The calculation for EQ-5D-5L index value will be performed according to EuroQol group's EQ-5D-5L User Guide (http://www.euroqol.org/about-eq-5d.html).

As suggested in the EQ-5D-5L User Guide (http://www.euroqol.org/about-eq-5d.html), the EQ-5D-5L descriptive scores and their dichotomized levels (No problems, Problems) within each EQ-5D dimension (mobility, self-care, usual activity, pain/discomfort, anxiety/depression), during the first 6 months, will be summarized by time (ie, visit/treatment cycle) descriptively, using counts and proportions. The EQ-5D-5L index value and VAS and their respective changes from baseline during the first 6 months will be summarized by time (ie, visit/treatment cycle) using means, standard deviations, medians and quartiles.

In addition, the changes from baseline (post baseline value - baseline value) of EQ-5D-5L index value, and separately EQ VAS, will be analyzed using a mixed model approach for repeated measures. This model will include the following terms as fixed effects: baseline value, treatment, time, and treatment-by-time interaction. The unstructured covariance matrix will be used to account for the within subject correlation and allow for different variances at different measurement times. The difference of the least squares means between the two treatment groups at each time (ie, visit/treatment cycle) and its corresponding 95% CI will be provided.

7.3.10 Duration of Complete Response

Duration of CR (in number of days) will be calculated from the first time a CR is observed to time of relapse (defined as the earliest time point whereby BM assessment or PB assessment indicate relapse/disease progression due to reappearance of leukemic blasts in PB or ≥5% leukemic blasts in BM; see Section 7.3.6). The duration of CR will be censored at the last available time point at which a relapse/disease progression was not observed. Duration of CR will be estimated using a Kaplan-Meier method for subjects who achieved a CR during the study.

The median and quartiles of duration of complete response, as well as their respective 95% CIs will be provided.

To take all subjects in the Efficacy Analysis Set into consideration when analyzing duration of CR, a separate Kaplan-Meier analysis including all subjects will be conducted with a 0-day event duration assigned to subjects who did not achieve a CR. The median and quartiles of duration of complete response, as well as their respective 95% CIs will be provided.

7.3.11 Subgroup and Exploratory Analysis

Subgroup analyses will be performed to explore the influence of the baseline variables, and the individual TC therapy administered, on the efficacy outcomes of CR rate and OS, and to evaluate the treatment effect at different levels of each baseline variable:

- Age (<75, ≥75).
- AML category (primary, secondary).
- Baseline cytogenetic risk (poor-risk, others [No/Unknown]).
- Baseline ECOG PS (0-1, 2-3).
- Baseline BM blasts (≤30%, >30%).
- Baseline total WBC counts (<20,000/μL, ≥20,000/μL).
- Study center region (North America, Europe, Asia-Pacific, ROW).
- Race (White, Black, Asian, Other).
- Presence of baseline genetic abnormalities such as FLT3, NPM1, and CEBPA (for each gene: yes, no).
- Individual TC (cytarabine, decitabine, azacitidine) compared with guadecitabine treatment for subjects randomized under that preselected TC option.

For subgroup analysis of CR, the OR of guadecitabine versus TC and associated 95% CIs will be provided for subgroups defined by categories of each variable listed above (except Individual TC). The intention is to descriptively display the treatment effect for each of these subgroups on Forest plots.

For subgroup analysis of OS, the HR of guadecitabine versus TC and associated 95% CIs will be provided for subgroups defined by categories of each variable listed above (except individual TC). Again, the intention is to descriptively display the treatment effect for each of these subgroups on Forest plots.

In addition, the CR and OS will be compared between subjects who were randomized to guadecitabine versus those who were randomized to TC within the subjects who were preassigned to a particular TC treatment. This comparison will be done for each of the three preassigned TC patient groups separately.

7.3.12 Dealing with Technical Issues Caused by Small Cell Count

If technical issues (such as non-convergence or unstable variance) arise due to small cell counts caused by too many levels of stratification variables, the stratification variables will be collapsed in the following order, until the technical issues have been resolved:

1) Collapse North America and EU into one level of geographic region, resulting in a new two-level geographic region variable (North America/EU vs. ROW).
2) Collapse geographic regions completely (combine North America, EU and ROW).
3) Collapse geographic regions completely and collapse Age categories (≥75 and <75 years).

7.3.13 Dealing with Non-Proportional Hazards in OS and PFS Analyses

In supportive analyses, the proportional hazards assumption for treatment over time will be assessed by including (effect of) treatment as a time-dependent covariate in the Cox regression model. The Cox regression analysis will be conducted with the time-dependent covariate (Treatment*Log(time)) in the model, where the variable Treatment has two levels, guadecitabine or TC, and Log(time) is natural log of survival time. A below 0.05 *p* value of this test is an indicator that the proportional hazards assumption may not hold.

If the proportional hazards assumption does not hold, the following additional analyses will be conducted to assess the treatment effect over different time intervals or at different time points.

1) A piece-wise Cox model will be conducted for evaluating a separate HR for each piece or interval. The cut-off times for the piece-wise Cox model are >0 to 6 months, >6 to 12 months, >12 to 18 months, >18 to 24 months and >24 months. For ease of calculation, one month is defined as 30 days for analyses conducted in this study.

2) The survival rates between the two treatment arms at each of the 6-month, 12-month, 18-month, and 24-month time points will be evaluated for the treatment effect at these time points. The stratified Kaplan-Meier estimates of survival probabilities and the corresponding standard errors based on the Greenwood formula (Kalbfleisch and Prentice 1980) will be used for constructing this analysis.

7.4 Safety Variables and Analyses

All safety analyses will be performed using the Safety Analysis Set which includes data from all subjects who receive any amount of study treatment (guadecitabine or TC; see Section 5.3).

Safety is assessed by subject-reported and investigator-observed AEs, and 30-day and 60 day all-cause mortality, along with concomitant medications, physical examination, clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital signs, ECOG performance status, and ECGs. Safety is also assessed by exposure to guadecitabine or TC, reasons for discontinuation, deaths and causes of deaths.

All safety data collected during the study will be included in the study database. All safety data collected during the study will be used for generation of safety summary tables, with the exception of AEs and medications. The AE and medication summary tables will only include treatment-emergent AEs and concomitant medications as defined in Sections 7.4.2 and 7.4.4.

7.4.1 Study Treatment Exposure

Cycle 1 Day 1 is defined as the first day of study treatment after randomization; cycle days are counted sequentially thereafter. Cycle 2 Day 1 is the first day of Cycle 2 regardless of treatment delays. The designated cycle duration is 28 days but any cycle could be prolonged to >28 days to allow blood count recovery if deemed clinically necessary. This convention for determining the start and stop dates for cycles is maintained until treatment is permanently discontinued. For easy presentation, Cycle x Day y is often abbreviated as CxDy in this document and statistical outputs.

Frequency counts and percentages of dose cycles received, dose cycles delayed, and dose reduced cycles will be summarized by treatment group. Summary statistics of number of cycles received, as well as percentages of intended dose received, will also be provided by treatment group. Dose delayed cycles are identified by the study site and entered into the electronic data capture (EDC) system. A dose reduced cycle is defined as a cycle in which the dose was reduced by 20% or more, compared with the planned Cycle 1 dose. Percentage of intended dose is equal to actual total dose divided by planned total dose through the last treatment cycle. Both completed or partially completed dose cycles are counted in these summaries.

7.4.2 Adverse Events

AE terms reported by study subjects or observed by investigators will be mapped to the appropriate System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA). Severity of AE will be graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Treatment-emergent AEs are defined as events that first occurred or worsened after the first dose of study drug given on C1D1 until 30 days after the last dose of study treatment or the start of an alternative anti-leukemia treatment, whichever occurs first, with the following exceptions: events that occurred after 30 days beyond the last dose of study treatment or the start of an alternative anti-leukemia treatment will also be considered treatment-emergent if the events are both serious and related to the study treatment. For the purpose of determining whether an AE is a treatment-emergent AE, incomplete AE start and stop dates will be imputed conservatively following the data programming standards as detailed in the Astex Data Programming Conventions.

All AE data collected in the study database will be listed, including those that are not treatment emergent. However, safety tables will be generated based only on Treatment-emergent AEs.

An overall safety summary table containing counts and percentages of subjects with any AE, any AE Grade ≥3, AE leading to treatment discontinuation, any serious AE (SAE), SAE leading to death, and other subjects with an SAE will be produced by treatment group. A similar table with related AE counts will also be produced by treatment group. Related events are those that the investigator considered to be suspected to be related to study treatment as described in the study protocol.

The number and percentage of subjects experiencing AEs will be summarized by MedDRA SOCs (sorted alphabetically) with PTs sorted alphabetically within each SOC, and by CTCAE grade. The number and percentage of subjects experiencing AEs will also be summarized by PT and sorted by event frequency. Related AEs, serious AEs, and related serious AEs will be summarized similarly. In summarizing AEs, if a subject reports the occurrence of a particular AE more than once, the event is only counted once with its worst CTCAE grade.

Treatment-site events (including events at the injection site) are of special interest. These events will be tabulated separately. Since it is expected that SC administration will be associated with more injection site events, a separate table will be produced to compare guadecitabine SC injection events to low dose Ara C (LDAC) SC injection events in subjects randomized under the preselected LDAC TC; and a similar table comparing guadecitabine SC to azacitidine (only those subjects receiving azacitidine by SC route) under the preselected azacitidine TC option.

7.4.3 30- and 60-Day All-cause Mortality

The percentage of 30- and 60-day all-cause mortality will be calculated based on each subject's date of death relative to C1D1 (ie, date of death minus date of C1D1). Subjects who died within 30 days will also be included in the 60-day mortality calculations. To avoid using a different denominator for calculation of the percentage of 30- and 60-day mortality, subjects who were lost-to-follow-up within 30- or 60-days from C1D1 (assumed to be a very small number, if any) will be considered alive for the corresponding 30- and 60-day mortality calculations. Causes of death and relationship to study treatment will also be summarized.

7.4.4 Concomitant Medications

Medications will be coded by the WHO Drug Dictionary.

Concomitant medications are the medications taken with a start date on or after the start of the administration of study treatment (C1D1), or those with a start date before the start of the administration of study treatment (C1D1) and a stop date on or after the start of the administration of study treatment (C1D1). Medications taken beyond 30 days from the last dose of study treatment or after the start of an alternative anti-leukemia treatment are not considered concomitant medications, unless they are used for treating a related SAE.

For the purpose of determining whether a medication is a concomitant medication, incomplete medication start and stop dates will be imputed conservatively following the data programming standards as detailed in the Astex Data Programming Conventions.

Concomitant medications will be summarized by WHO Drug Dictionary Therapeutic Subgroup (ATC level 2) and Drug Name, sorted alphabetically, using counts and percentages.

Special interest concomitant medications include anti-emetic drugs, growth factors, broad-spectrum antibiotics, and antifungals. These concomitant medications will be tabulated separately. Transfusions will be described separately as part of the efficacy analyses (Section 7.3.8).

7.4.5 Laboratory Tests

Data from different local laboratories will be standardized to consistent SI units, and presented in data listings. Laboratory values recorded as an interval such as "≥x", "<x", or "2+" will be handled, if necessary for calculation purposes, following the data programming standards as detailed in the Astex Data Programming Conventions.

Laboratory values will be graded, if relevant and possible, by CTCAE version 4.03 in conjunction with the Harrison (18th edition) lab book normal values (Longo et al 2011). Shift tables will display (1) shift from baseline grade to the worst grade during the study, and (2) shift from baseline grade to the last grade at the end of study.

7.4.6 Vital Signs

Vital signs will be summarized by visit using the proportion of subjects who have vital sign values too high or too low, according to the conventionally accepted vital sign normal ranges as listed below:

- Pulse rate ≥110 bpm.
- Pulse rate ≤50 bpm.
- Diastolic blood pressure ≥110 mmHg.
- Diastolic blood pressure ≤55 mmHg.
- Systolic blood pressure ≥180 mmHg.
- Systolic blood pressure ≤80 mmHg.
- Respiration rate ≥20 breaths/min.
- Body temperature ≥39°C.

7.4.7 Electrocardiogram

At each ECG assessment time point (pre- and post-dose on Day 1 of Cycle 1 and on termination visit), the mean of the available electrocardiogram values (repeated three times) will be calculated and used in data listings and summary tables as the actual value for that assessment.

The following data listings will be provided to assist the medical assessment of the ECG outcomes:

- All laboratory electrocardiogram values, including the calculated mean value of each triplicate at each time point.
- All subjects who had a QTc >500 ms or >60 ms increase from baseline including the associated baseline values.

QTc values will also be graded based on CTCAE, and the shift table showing the shift from baseline grade to the worse grade, and from baseline grade to the last grade will be provided.

7.4.8 ECOG Performance Status

ECOG performance status will be summarized by visit, at all scheduled visits where performance status was assessed, using counts and percentages.

7.4.9 Physical Examination

Physical examination data will be presented in a data listing.

7.5 Pharmacokinetics Analysis

PK parameters will be derived using noncompartmental analyses for each subject for whom sparse PK samples were collected and successfully analyzed (PK Analysis Set; see Section 5.4). Descriptive statistics will include mean, standard deviation, minimum, median, and maximum for guadecitabine and decitabine PK parameters.

The relationship between [redacted] will be assessed based on the PK data and efficacy/safety data collected in this study. The methods will include a population PK modeling approach using the sparse data collected. The details of population PK modeling and full results of the [redacted] analyses will be reported in a separate document, and the summary of key findings will be included in the clinical study report.

7.6 Interim Analyses and Data Monitoring

Data will be reviewed by an independent DMC at regular intervals primarily to evaluate safety during study conduct. The committee will operate independently from the Sponsor and the clinical investigators.

One formal interim analysis of OS is planned, providing the DMC a chance to recommend stopping the trial earlier in case the study treatment shows an overwhelming effect on survival. This interim analysis will be conducted by the independent DMC after approximately half (ie, approximately 335) of the required death events have occurred using the same statistical methods as described in Section 7.3. All data available at the time of clinical data cut for the interim analysis will be included in the interim analysis. Inclusion of additional available data beyond the clinical data cut will be at the discretion of DMC. The nominal alpha values for the interim and final OS analyses are based on Lan-DeMets implementation of the O'Brien-Fleming boundary (Lan and DeMets 1983; O'Brien and Fleming 1979). With one interim analysis at 50% information time point plus one final analysis, the 2-sided alpha-boundaries are 0.00014 and 0.00995, respectively.

If the trial continues after the interim analysis, and if the primary analysis of CR rate is significant at the 0.04 level, the alpha level for the primary analysis of OS will be $0.04+0.00995=0.04995\approx0.05$. If the trial continues after the interim analysis, and if the primary analysis of CR rate is not significant at the 0.04 level, the alpha value for the primary analysis of OS will be $0.00995\approx0.01$. The overall alpha error is controlled at the 0.05 level.

In the unlikely scenario of having observed a significant ($p\leq0.00014$) positive OS result at the planned interim analysis time point with an acceptable safety profile of guadecitabine, the DMC may choose to analyze the co-primary endpoint CR at an appropriate alpha level to be determined by DMC before making a recommendation to the Company. The Company does not intend to announce the interim analysis results and make any decision to prematurely terminate the study, for any reason other than major safety concerns, without discussing the data and recommendation from the DMC first with the major regulatory agencies.

7.7 Handling of Missing Data and Other Data Anomalies

No missing data imputations are planned for the study, except as specified. Subjects lost to follow-up will be included in statistical analyses to the point of their last evaluation.

7.8 Handling of Protocol Deviations

Protocol deviations that occur during the study are captured by study monitors and recorded in the CRO's clinical trial management system. Study medical monitors conduct regular reviews of all recorded protocol deviations to ensure the quality conduct of the study. Study medical monitors also identify and categorize important protocol deviations. Important protocol deviations will be summarized by deviation category using counts and percentages. A data listing of all important protocol deviations will also be provided.

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