16.1.9 Statistical Analysis Plan

Statistical Analysis Plan (22 July 2020)

SGI-110-06

Statistical Analysis Plan

A Phase 3, Multicenter, Randomized, Open-Label Study of Guadecitabine (SGI-110) versus Treatment Choice in Adults with Previously Treated Acute Myeloid Leukemia

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Based on: Protocol Amendment 4.0

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ABBREVIATIONS AND DEFINITIONS

AE	adverse event
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
BM	bone marrow
BSA	body surface area
BSC	best supportive care
CDA	cytidine deaminase
CI	confidence interval
C_{max}	maximum concentration
CR	complete response
CRc	composite CR (CRc = CR + CRp + CRi)
CRh	Complete response with partial hematologic recovery
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
EFS	event-free survival
EQ VAS	EuroQol visual analogue scale
FLAG/FLAG-Ida	fludarabine, cytarabine, G-CSF, +/- idarubicin
HCT	hematopoietic cell transplant
HiDAC	high dose cytarabine
HMA	hypomethylating agent
HR	hazard ratio
ITT	intent-to-treat
IV	intravenous
IWG	International Working Group
LDAC	low-dose cytarabine
MDS	myelodysplastic syndromes
MEC	mitoxantrone, etoposide, and cytarabine
MedDRA	Medical Dictionary for Regulatory Activities
NCCN	National Comprehensive Cancer Network
NDAOH	number of days alive and out of the hospital
NE	nonevaluable
NR	nonresponder
OR	odds ratio
OS	overall survival
PB	peripheral blood
PK	pharmacokinetic(s)
PR	partial response
PT	preferred term
QOL	quality of life
QTc	heart rate corrected QT interval
RBC	red blood cell
ROW	rest of world
Remission	equivalent to “response”
Response	equivalent to “remission”
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SGI-110	guadecitabine
SOC	system organ class
TC	treatment choice
WBC	white blood cell

1.0 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on SGI-110-06 protocol version 4.0, dated 29 October 2018. Based on data from 278 randomly assigned subjects, the Data Monitoring Committee (DMC) recommended stopping further enrollment into the trial based on futility analysis that indicated the trial was unlikely to show superiority of guadecitabine over treatment choice (TC) for overall survival (OS). Consequently, the study was closed to further enrollment in September 2018 (protocol amendment 4).

Analyses and statistical reporting for SGI-110-06 will be conducted by Astex Pharmaceuticals Biostatistics department with the interim analysis results as reported by the study's DMC. The analyses specified in this document supersede the high-level analysis plan described in the protocol.

1.1 Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is the most common acute leukemia diagnosed in adults. The average age of a patient with AML is about 68 years; AML is generally a disease of older people and is uncommon before age 45 (American Cancer Society 2020).

AML is differentiated from other hematopoietic malignancies by the presence of greater than 20% myeloblasts in the bone marrow or blood. In AML, myeloblasts crowd out normal hematopoietic cells in the bone marrow, leaving the patient with insufficient erythrocytes, platelets, and neutrophils. The consequent pancytopenia causes most of the symptoms of leukemia. Diagnosis is made by pathologic examination of peripheral blood (PB) and bone marrow (BM), and no opportunity for early detection exists except in patients with antecedent hematologic malignancies or inherited disorders. Diagnosis of AML requires a rapid assessment and initiation of treatment. AML leads to death within a few weeks to months after diagnosis if left untreated.

1.2 Treatment Options

The standard intensive induction chemotherapy for AML has been the same for decades. Although up to 80% of AML patients <60 years of age will achieve complete response (CR) with intensive chemotherapy, approximately 30% to 40% of these patients will die from their disease (Roboz 2011; Estey 2012). The outlook for patients >60 years old is significantly worse. Only 45% to 50% of older patients achieve complete remission and most remitting patients quickly relapse.

Patients unable to achieve a CR with standard induction therapy (refractory AML) or whose disease returns after achieving remission (relapsed) are likely to die from their disease (Estey 2012). There are no proven treatment options for subjects with AML refractory to intensive remission induction chemotherapy or for subjects who relapse after intensive chemotherapy treatment(s), particularly if they fail re-induction with the standard regimen.

There are several commonly used salvage regimens, most of which include cytarabine as either a single agent or in combination regimens (NCCN AML Guidelines 2014). The hypomethylating

agents (HMAs) decitabine and azacitidine, though mostly studied in myelodysplastic syndromes (MDS) and newly diagnosed AML (Kantarjian et al 2012, Fenaux et al 2010, Lubbert et al 2012), are often considered an option for frail, older patients with relapsed/refractory AML (Roboz et al 2014). Due to the lack of proven treatment for r/r AML, enrollment in a clinical trial is considered an appropriate strategy (NCCN AML Guidelines 2014; Roboz et al 2014).

1.3 Guadecitabine

Guadecitabine is a new chemical entity that incorporates decitabine and deoxyguanosine linked by a phosphodiester bond. Unlike decitabine, guadecitabine is resistant to deamination by cytidine deaminases (CDAs). Compared with intravenous (IV) decitabine, decitabine from subcutaneous (SC) guadecitabine had prolonged exposure and lower maximum concentration (C_{max}) (Issa et al 2015). This differentiated pharmacokinetic (PK) profile is the proposed basis for potential enhancement of clinical activity of guadecitabine.

Clinical responses in subjects with AML (including relapsed/refractory AML) and MDS have been observed in the Phase 1-2 study (SGI-110-01) (Issa et al 2015; Kantarjian et al 2013). The median overall survival was estimated to be 6.6 months for subjects with r/r AML (SGI-110-01).

Two additional Phase 3 studies (SGI-110-04 and SGI-110-07) of guadecitabine versus treatment choice (TC) were conducted. SGI-110-04 was in adults with previously untreated AML who were unfit to receive or who were not considered candidates for intensive induction chemotherapy. SGI-110-07 (currently ongoing) is in adults with MDS or CMML who failed or relapsed after prior treatment with azacitidine, decitabine, or both.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

To assess and compare overall survival (OS) between guadecitabine and treatment choice (TC) in adults with previously treated AML.

2.2 Secondary Objectives

To assess and compare effects of guadecitabine and TC in adults with previously treated AML with respect to the following variables:

- Event-free survival (EFS).
- Long-term survival.
- Number of days alive and out of the hospital (NDAOH).
- Transfusion needs.
- Complete response (CR) and CR with partial hematologic recovery (CRh) rates.
- Composite CR rate (CRc). CRc = CR + CR with incomplete blood count recovery (CRi) + CR with incomplete platelet recovery (CRp).

- Bridge to hematopoietic cell transplant (HCT).
- Health-related quality of life (QOL).
- Safety.

[redacted]

3.0 STUDY DESIGN

3.1 Overall Study Design

This is a Phase 3, randomized, open-label, parallel-group multicenter study of the efficacy and safety of guadecitabine in adults with previously treated AML. Approximately 404 subjects from approximately 100 study centers were planned to be randomly assigned to either guadecitabine or TC in a 1:1 ratio (approximately 202 subjects per group):

- Guadecitabine: 60 mg/m^2 in 28-day cycles (either given for 10 days on Days 1-5 and Days 8-12 or on Days 1-10 [Cycle 1], for either a 5-day regimen [Days 1-5] or a 10-day regimen [Days 1-5 and Days 8-12 or on Days 1-10] for Cycle 2, based on assessment of disease response and hematological recovery at the end of Cycle 1, and then for 5 days only [Days 1-5] for Cycles >2).
- TC (high intensity, low intensity, and best supportive care)

Before randomization, the investigator assigns each subject to one of the following TC options based on the subject's prior treatment received, country approval, and local institutional standards:

- High intensity: intermediate or high dose cytarabine (HiDAC); mitoxantrone, etoposide, and cytarabine (MEC); or fludarabine, cytarabine, G-CSF, +/- idarubicin (FLAG/FLAG-Ida).
- Low intensity: low dose cytarabine (LDAC), decitabine, or azacitidine.
- Best supportive care (BSC).

Randomization was stratified by intensity of preselected TC option (high intensity vs low intensity vs BSC), Eastern Cooperative Oncology Group (ECOG) performance status (0-1 vs 2), baseline cytogenetics (poor risk vs other), and study center region (North America vs rest of world [ROW]).

Subjects with a different selection of TC intensity may expect a different treatment outcome, with younger and healthy subjects usually being treated with a higher intensity TC and experiencing a better treatment response and longer survival. Subjects who have a poor performance status (2) tend to have a worse survival than subjects with a good performance status (0 or 1). Similarly, subjects with a poor-risk cytogenetics generally do not respond to treatment well and have a shorter

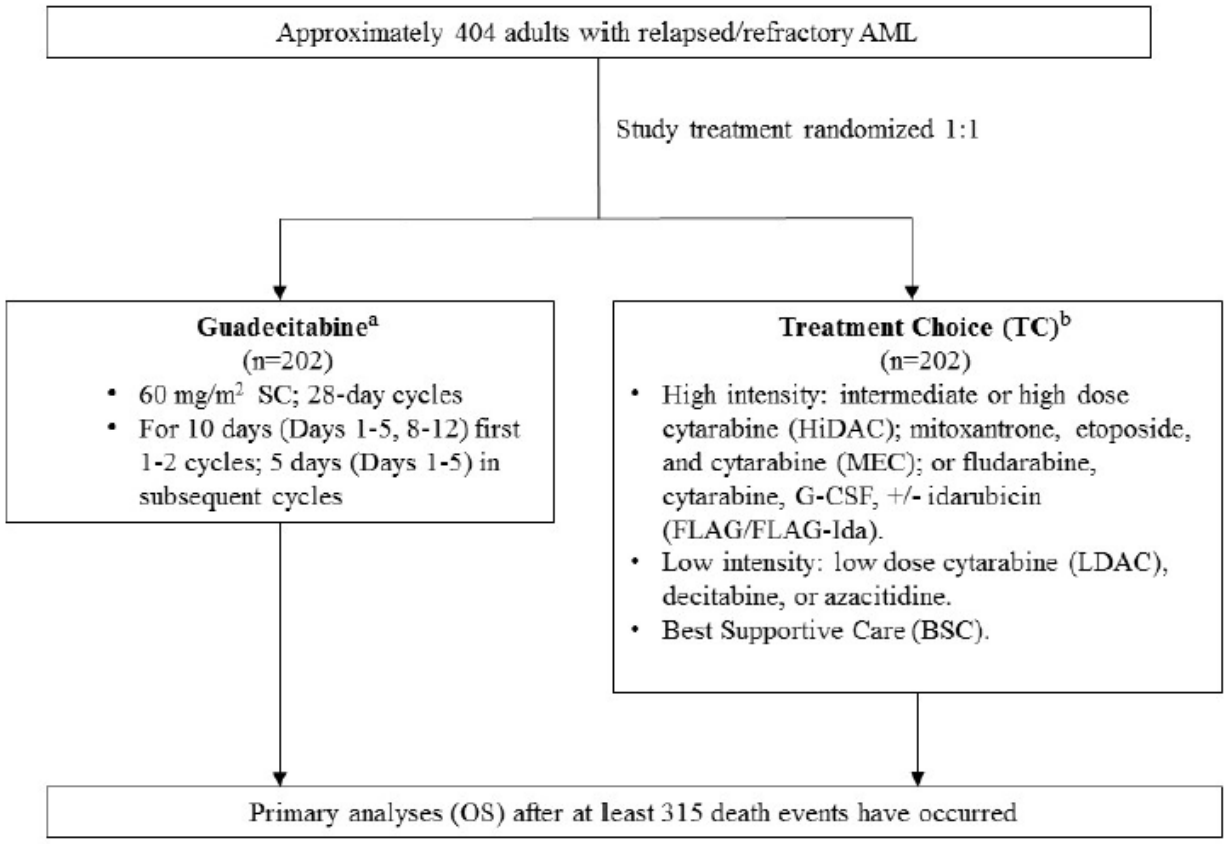
survival time. In addition, prognosis could have regional differences due to multiple factors including variable levels of standard of care. Stratification by these known and important prognostic factors measured at baseline sought to minimize imbalance between treatment groups within strata and was designed to reduce bias and improve power of the study.

Selection of one of the TCs was 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).

Peripheral blood (PB) was assessed at Screening and on Day 1 of each cycle for response evaluation. Bone marrow (BM) aspirate or biopsy was performed at screening and then at the end of Cycles 1, 3, and 6 unless PB showed persistence of ≥5% leukemic blasts that excluded the possibility of a marrow response. After Cycle 6, BM assessment, BM aspirate, or biopsy (with touch prep slides) was repeated every 3 months for the first year on study and then every 6 months thereafter until PB or BM assessment showed disease progression or relapse.

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 disease 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. TC duration will be based on approved local prescribing information and institutional standard practice.

3.2 Study Endpoints

3.2.1 Primary Efficacy Endpoint

- OS, defined as the number of days from date of randomization to date of death.

3.2.2 Secondary Efficacy Endpoints

- EFS defined as the number of days from randomization to the earliest date of, treatment discontinuation (for reasons other than initiation of HCT), start of alternative anti-leukemia therapy (except for HCT), or death.
- Survival rate at 1 year after randomization. (Subjects will also be followed long term to estimate 2-year survival rate.)

- NDAOH.
- Transfusion independence rate, calculated based on the number of subjects with neither red blood cell (RBC) nor platelet transfusion for any period of 8 weeks after treatment.
- CR rate based on modified International Working Group (IWG) 2003 AML Response Criteria and CRh rate as described in the US FDA approved Prescribing Information of enasidenib and ivosidenib.
- CRc (CR+CRi+CRp) rate.
- HCT rate. (In subjects who undergo HCT, time to stem cell engraftment and 100-day mortality rate post HCT will also be assessed.)
- Duration of combined CR and CRh, defined as the time from first CR or CRh to time of relapse.
- Health-related QOL by EQ-5D (consisting of the EQ-5D-5L descriptive system and the EQ visual analogue scale [VAS]).

3.2.3 Safety Endpoints

Safety was assessed by subject-reported and investigator-observed AEs and 30- and 60-day all-cause mortality, along with clinical laboratory tests (hematology, chemistries), concomitant medications, physical examination, vital signs, ECOG performance status, and ECGs.

4.0 SAMPLE SIZE

In order to provide power of at least 90% to detect a difference in hazard ratio of approximately 0.692 (median OS of 4.5 months for the TC arm versus 6.5 months for the guadecitabine arm) using a stratified 2-sided log-rank test at an overall 0.05 alpha level given the 1:1 randomization, the trial will require 315 death events. Assuming that the enrollment would be non-uniform over an 18 month period during which 3 to 29 subjects per month (3, 6, 9, 12, 15, 18, 21, 24, 27, and 29) were expected to be enrolled in the first 10 months in increasing order followed by 30 subjects per month in months 11-18, with the proportion of subjects dropping out each month equal to 0.012, then approximately 404 subjects would need to be randomized. If after a follow up of 12 months from the last patient randomized, the 315 death events had not occurred, the primary analysis would be conducted at 12 months from last subject randomized (if 277 or more death events have occurred), or after at least 277 death events had been observed (corresponding to 86% power). Based on DMC recommendation to stop further enrollment, the time of primary analyses was shifted to occur after approximately 12 months follow-up from the last subject randomly assigned to treatment or after the last subject is off study.

5.0 ANALYSIS SETS

5.1 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, 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 monthly whether or not they are still on study treatment. Secondary analysis, if performed, may also include data beyond the first 6 months of the study (eg, over the entire study period until disease progression).

5.2 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 a subject receives more than one type of study treatment during the study, the subject will be included in the treatment group according to the treatment received most frequently. In the unlikely event a subject receives the same number of cycles of two different treatments the subject will be included in the treatment group according to the treatment received first.

[redacted]

6.0 SCHEDULE OF ANALYSES

Data listings and summary tables were 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 were generated by

Axio Research LLC, an independent contract research organization (CRO) supporting the DMC activities.

One formal interim analysis of OS was planned to be conducted by the DMC when approximately half of the required 315 death events have occurred.

At the Sponsor's request, an additional earlier interim analysis of futility was conducted by the DMC at one of the scheduled DMC meetings on 12 September 2018 when approximately one-third of the required 315 death events had occurred. This interim analysis was added due to the emerging information showing a lack of significant survival benefit over the TC arm (similar to the Low Intensity TC in this study) from a similar trial conducted by the Sponsor in treatment-naive AML subjects using the same drug product in which the study failed to meet the primary endpoint (SGI-110-04 study). This meeting resulted in a DMC recommendation to the Sponsor that enrollment in Study SGI-110-06 should be discontinued based on futility.

Since the enrollment was stopped prior to reaching the planned number of death events for the formal interim analysis of OS as described in the protocol, the formal interim analysis was cancelled.

As a result, the time of primary analyses was shifted to occur after approximately 12 months follow-up from the last subject randomly assigned to treatment or after the last subject is off study. A cutoff date of 20 January 2020 was planned to support the primary analysis and subjects who were no longer receiving study treatment were not followed for survival beyond the cutoff date. The database lock based on the 20 January 2020 cutoff date was delayed due to the COVID-19 pandemic and a final database lock will be conducted which will include all data from all subjects up to the time they discontinued from the study or completed participation in SGI-110-06 and enrolled into the extension study, SGI-110-12. This final study database will include data beyond the 20 January 2020 data cutoff date for subjects who were still participating in SGI-110-06. To avoid bias related to the changes in data collection after 20 January 2020, key primary and secondary endpoints such as overall survival, event-free survival, survival rate at 1 year after randomization, transfusion independence rate, response rates and duration of response will be based on data up to the planned data cutoff date, while analyses of all other efficacy and safety endpoints will be based on all data included in the final study database.

7.0 STATISTICAL ANALYSIS

Unless otherwise specified, treatment comparisons will be performed between the guadecitabine group and the TC group. Additional comparisons of guadecitabine with each TC option in the patients randomized under that preselected TC option may be performed as appropriate. Procedures will be employed to control the alpha error associated with testing multiple endpoints (see Section 7.3.3). The statistical test to be employed for each comparison is specified below. The SAS® statistical package (SAS Institute Inc., Cary, NC, USA, version 9.4 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, individual efficacy data, subjects excluded from the efficacy analysis, AEs, medications, and the relevant laboratory measurements. Additional data listings may be generated to support other relevant discussions in CSR.

The baseline value for a particular variable is generally the last value collected prior to the Cycle 1 Day 1 (C1D1) study visit. For subjects who were randomized but did not receive study treatment, the baseline value is defined as the last value collected prior to randomization. For variables collected on Day 1 of Cycle 1 (C1D1) without explicit timing, the C1D1 values will be used as the baseline values since the protocol requires these tests or procedures to be performed prior to dosing.

7.1 Subject Disposition

Subject disposition including numbers randomized, treated, and treatment discontinuation by reason, as well as the reasons for withdrawal from study will be summarized by treatment group using frequencies and percentages based on information collected on the relevant study case report form pages. The number of subjects screened, screen failures and reasons for failure will be summarized. The number of subjects randomized will also be tabulated by region, country, study site/investigator and treatment group. The number of subjects in each analysis set will be summarized by treatment group, when applicable. In addition, subject eligibility information including characteristics related to inclusion and exclusion criteria collected during screening will be summarized by treatment group.

Duration of follow-up will be calculated as the (date of the data cutoff − date of randomization) and will be summarized using mean, standard deviation, median, minimum, and maximum.

7.2 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics include, but are not limited to age, sex, ethnicity, race, geographical region, response to initial intensive induction therapy, time since AML diagnosis, height, weight, body surface area (BSA), ECOG performance status, number and type of prior cancer therapies, 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, TP53, FLT3-ITD, NPM1, ASXL-1, RUNX-1, and CEBPA biallelic.

Categories of response to initial intensive induction therapy are defined as follows:

- Refractory is defined as refractory to induction where a subject did not have CR, CRp, or CRi to the first line induction regimen.
- First relapse refers to subjects who had just one prior regimen and had a response (CR, CRp, CRi, or PR) to the first line induction regimen.

- >1 relapse refers to subjects who had at least 2 prior regimens and had a response.

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.

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

Unless otherwise specified, all efficacy analyses will be based on the Efficacy Analysis Set. This section describes the analyses conducted at the final and primary analysis time point after at least 12 months follow-up from the last subject randomly assigned to treatment. The stratification factors used in the analyses will be the randomization stratification factors unless it is necessary to collapse some strata due to analysis difficulties caused by too many strata. The rule for collapsing strata are detailed in Section 7.3.5. If the strata are collapsed for the analysis of the primary endpoint, the collapsed strata will be applied to stratified analyses for all subsequent endpoints.

7.3.1 Primary Efficacy Endpoint and Analyses

OS is the primary efficacy endpoint and is defined as the time, in days, from the subject randomization date to the date of death (regardless of cause).

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

In the absence of death at the time of analysis, the survival time will be censored on the last date the subject is known to be alive. Subjects who do not have post-baseline information will be censored at the date of randomization.

OS curves will be estimated using the Kaplan-Meier method and formally compared between the two treatment groups using a 2-sided stratified log-rank test, stratified by the randomization stratification factors.

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

OS will be tested at an overall alpha level of 0.05, as further described in Section 7.3.3. If this primary endpoint reaches statistical significance at this level in favor of guadecitabine, then the study will be considered positive for efficacy.

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.

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.

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

1) 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 OS, based on treatment actually received as described in Section 5.2, 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) An 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 (except hematopoietic cell transplant [HCT]).

7.3.2 Secondary Efficacy End Points and Analyses

Secondary efficacy endpoints include EFS, survival rate at 1 year and 2 years after randomization, NDAOH, transfusion independence rate, combined CR + CRh rate, CRc rate and HCT rate, duration of combined CR and CRh, and the EQ-5D-5L descriptive system and the EQ VAS.

7.3.2.1 Event-Free Survival

Event-free survival (EFS) is defined as the time, in days, from the subject randomization date to the earliest of treatment discontinuation (for reasons other than initiation of HCT), start of alternative anti-leukemia therapy (other than HCT), or death.

In the absence of any of these events at the time of analysis, event-free survival time will be censored on the last date the subject is known alive. Subjects who do not have post-baseline information will be censored at the date of randomization.

EFS curves will be estimated using the Kaplan-Meier method and formally compared between the two treatment groups using a 2-sided log-rank test, stratified by the randomization stratification factors. EFS will be tested at an overall alpha level of 0.05, as further described in Section 7.3.3.

The median (and quartiles) duration of EFS and the associated 95% CI for each treatment arm will be estimated using the Kaplan-Meier method and the log-log transformation for the event-free survival function.

7.3.2.2 Survival Rate at One-Year and Two-Years

One-year survival rate is defined as the survival rate at the end of the first year from randomization. One-year survival rate for each treatment group will be estimated by Kaplan-Meier procedure as addressed in Section 7.3.1. Hypothesis testing will be based on the stratified Kaplan-Meier estimates and standard errors estimated by the Greenwood formula using the log-log transformation of the OS function at an overall alpha level of 0.05, as further described in Section 7.3.3. Subjects who do not have death in record will be censored on the last date known to be alive. The stratification factors will be the same as those used in the OS analysis.

The survival rate at 2 years will be similarly summarized.

7.3.2.3 Number of Days Alive and Out of the Hospital

The date of each hospital admission and discharge were collected for each subject for at least 6 months (and until disease progression for subjects who had not progressed during the first 6 months or until the subject died or withdrew consent prior).

The duration of each individual hospital stay in days (regardless of the reason for hospitalization) is calculated as:

$$\text{Duration of individual hospital stay} = \text{date of discharge} - \text{date of admission}$$

For a subject who was 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 the durations of all individual hospital stays occurring between date of randomization 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:

$$\text{NDAOH6M} = 180 - \text{total duration of all hospital stays} - \text{number of death days before Day 180}$$

For subjects who died within the first 6-month period, the number of death days before Day 180 is calculated as:

$$\text{Number of death days} = (\text{date of Day 180} - \text{date of death})$$

For subjects who died on or after Day 180 the number of death days before Day 180 will be set to 0.

For subjects who were 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 NDAOH6M will be summarized by treatment group and comparisons between the 2 treatment groups will be performed using an analysis of variance (ANOVA) model at an overall alpha level

of 0.05, as further described in Section 7.3.3. The variables used for stratification at randomization will be included in the analysis of variance model as fixed factors.

7.3.2.4 Transfusion Independence Rate

Transfusion independence rate is calculated as number of subjects with neither RBC nor platelet transfusion for any period of 8 weeks after the initiation of treatment (or C1D1 visit date for subjects randomized to BSC or randomization for subjects not treated) and up to treatment discontinuation divided by the total number of subjects included in the efficacy analysis. The transfusion independence rate will be compared between the 2 treatment groups using a Cochran Mantel-Haenszel test stratified by the randomization stratification factors at an overall alpha level of 0.05, as further described in Section 7.3.3. In addition, the Mantel-Haenszel weighted difference in transfusion independence rate between the 2 treatment groups and the associated CI will be provided.

The individual RBC and platelet transfusion independence rates will also be presented.

7.3.2.5 Criteria for Response Assessment

The 2003 AML IWG Response Criteria (summarized in Table 1) are used to identify AML subjects with CR, CRp, CRi, or partial response (PR). CRh will also be assessed as a subset of CRi or CRp who have partial hematologic recovery and is defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/μL and ANC >500/μL). Evaluation of response will be conducted by Astex medical monitors assisted by programmed data listings.

Table 1: 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 who did not receive any study treatment, or who do not have a valid post-treatment (or post C1D1 visit date for BSC) efficacy assessment (ie, no post-treatment BM/PB sample or the quality of BM/PB sample is not adequate for an assessment of efficacy) will be classified as not evaluable (NE) for response classifications. These subjects will be included in the denominator of the ITT analysis for calculation of response rates. Subjects who cannot be classified into a response category (CR, CRp, CRi, CRh, or PR) or into the NE category will be classified as non-responders (NR) for a given evaluation time point. For subjects who experience different response levels at different visits, the best response in the order of CR, CRp, CRi, and PR will be used for summary and analyses. Subjects who progress (see Section 7.3.2.1 for definition) prior to experiencing a response (CR, CRp, CRi, CRh, or PR) will be included in the NR category. The best response (CR, CRp, CRi, PR, NR, or NE) based on the investigators will be summarized in a table displaying the number and percentage of subjects who meet the criteria for each endpoint. CRh, which is a subcategory of CRp and Cri, will be summarized similarly.

7.3.2.6 Complete Response and Complete Response with Partial Hematologic Recovery Rates

The CR and CRh rates are calculated individually and combined as the number of subjects who achieve a best response of CR or CRh, divided by the total number of subjects included in the efficacy analysis. The CR, CRh, and combined CR+CRh rates will be compared between the 2 treatment groups using a Cochran Mantel-Haenszel test, stratified by the randomization stratification factors, at an overall alpha level of 0.05, as further described in Section 7.3.3. In addition, the 2-sided 95% CI for the Mantel-Haenszel weighted difference in CR, CRh, and combined CR+CRh rates between the 2 treatment groups will be provided.

7.3.2.7 Composite CR Rate

The CRc rate is calculated as the number of subjects who achieve 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, stratified by the randomization stratification factors, at an overall alpha level of 0.05, as further described in Section 7.3.3. In addition, the 2-sided 95% CI for the Mantel-Haenszel weighted difference in CRc rate between the 2 treatment groups will be provided.

7.3.2.8 HCT

The HCT rate will be calculated as the number of subjects who received an HCT after randomization divided by the total number of subjects included in the efficacy analysis. The HCT rate will be compared between the 2 treatment groups using a Cochran Mantel-Haenszel test stratified by the randomization stratification factors, at an overall alpha level of 0.05, as further described in Section 7.3.3. The Mantel-Haenszel weighted difference in HCT rate between the 2 treatment groups and the associated CI will also be provided.

Time-to-stem-cell engraftment is calculated, for subjects who received an HCT after randomization, from the day of transplant to the day of engraftment, as recorded in the CRF. The day of engraftment is the first day of 3 consecutive days of PB absolute neutrophil counts of >500/μL. The number and percent of subjects who received HCT and subsequently achieved stem-cell engraftment will be summarized by treatment group. The time-to-stem-cell engraftment will also be summarized by treatment group using mean, standard deviation, median, minimum, and maximum for subjects who have achieved stem-cell engraftment.

In addition, 100-day post-HCT mortality rate (regardless of cause) will be calculated for subjects who received an HCT after randomization and summarized by treatment group. The mortality rate will be number of subjects who died from any cause within 100 days of HCT divided by the total number of subjects who received HCT. HCT subjects who had no survival status data on or after 100 days post HCT will be excluded from the analysis.

7.3.2.9 Duration of Combined CR and CRh

A combined duration of CR and CRh (in number of days) will be calculated from the first time a CR or CRh is observed to the date of the earliest of the following 3 events: (1) relapse (defined as the earliest time point whereby BM assessment or PB assessment by the investigator indicate relapse/disease progression due to confirmed reappearance of leukemic blasts in PB or ≥5% leukemic blasts in BM, or clinical progression determined by the investigator), (2) start of alternative therapy (except HCT) or (3) death. In the absence of any event, the combined duration of CR and CRh will be censored at the last available time point (BM assessment, PB assessment, or safety/long-term follow-up visit) at which an event was not observed. Duration of combined CR and CRh will be analyzed using the Kaplan-Meier method for subjects who achieved a CR or CRh during the study and compared between the two treatment groups using a non-stratified log-

rank test. The median and quartiles of duration of complete response, as well as their respective 95% CIs will be provided. Duration of CR will be calculated and analyzed similarly.

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

In addition, both time to first response and time to best response will be calculated and analyzed for subjects who achieve a response of CR, CRp, CRi, or PR. Time to first response is defined as the time, in days, from the date of first treatment (C1D1) to the first date when any response is achieved. Time to best response is similarly defined as the time, in days, from the date of first treatment (C1D1) to the first date when a subject's best response, in the order of CR, CRp, CRi, or PR, is achieved. The times to first response and best response will be summarized by treatment group using mean, standard deviation, median, minimum, and maximum. Time to CR will be summarized similarly.

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

The EQ-5D-5L descriptive system scores and the EQ VAS were collected for each subject for a minimum 6 months unless the subject died or withdrew 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). Since there are only a limited number of countries which have rules available for calculating EQ-5D-5L index values, the rules for England (Devlin et al 2016) will be used for all subjects from all countries in this study. These analyses will include only the data collected for each subject during the first 6 months of study participation.

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), 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 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.

7.3.3 Test Sequence and Procedures of Statistical Tests for Efficacy Endpoints

To control the alpha errors associated with testing the multiple endpoints, the primary endpoint, OS, will be tested first. If OS reaches statistical significance in favor of guadecitabine, a hierarchical analysis of secondary endpoints will proceed in the following pre-specified order:

1) EFS.
2) Survival rate at 1 year after randomization.
3) NDAOH during the first 6 months.
4) Transfusion independence rate.
5) Combined CR + CRh rate
6) CRc (CR+CRi+CRp) rate.
7) HCT rate.

A statistically significant test result in favor of guadecitabine for a given endpoint serves as a gatekeeper (Westfall and Krishen 2001) for the testing of statistical significance to proceed to a subsequent secondary endpoint. The overall alpha error rate is controlled at the 0.05 level by following the above testing sequence and procedures.

The efficacy endpoints of duration of combined CR and CRh and Health Related QOL will be used as supportive evidence of the beneficial treatment effect and will therefore, not be included in the hierarchical testing to control alpha error. Differences of treatment effect for these endpoints and associated 95% CIs, if applicable, will be constructed.

7.3.4 Subgroup [redacted] Analysis

Subgroup analyses will be performed to explore how the treatment effect on OS is influenced by baseline variables, extent of treatment received, and the individual TC therapy administered. To evaluate the treatment effect at different levels of each of these variables, the Kaplan-Meier analysis and Cox model will be performed separately by each level of each variable as follows:

- Age (<65, ≥65).
- Age (<75, ≥75).
- Sex (Male, Female).
- Baseline cytogenetic risk (poor-risk, others).
- Baseline ECOG performance status (0-1, 2).
- Response to initial intensive induction therapy (refractory, first relapse, >1 relapse).
- Prior HCT (yes, no).
- Baseline BM blasts (≤40%, >40%).

- Baseline PB blasts (≤30%, >30%).
- Baseline total WBC counts (≤20,000/µL, >20,000/µL).
- Study center region (North America, ROW).
- Race (White, Black, Asian, Other).
- Presence of baseline genetic mutations or gene expressions for each gene such as FLT3-ITD, NPM1, CEBPA biallelic, TP53, ASXL-1, and RUNX-1 (yes, no).
- Treatment cycles received (<4 cycles vs ≥4 cycles).
- Treatment cycles received (<6 cycles vs ≥6 cycles).
- Individual preselected TC (high intensity, low intensity, BSC).

The treatment effect (HR and 95% CI) for each of these subgroups will be displayed on Forest plots.

Subjects with missing a value for a variable used to define a subgroup will be excluded from that subgroup analysis except for subgroups with an "Other" category. In those subgroups, subjects with missing values will be included in the Other category.

[redacted]

7.3.5 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 pre-selected TC options (combine 2 or more of the TC comparators: high intensity, low intensity and BSC).
2) Collapse study center regions (combine North America and ROW) and collapse pre-selected TC options.

7.4 Safety Variables and Analyses

Unless otherwise specified, 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 5.2). For all safety analyses, summaries by treatment group (guadecitabine and TC) will be provided. Additional displays of study treatment exposure and adverse events may be generated for each preselected TC option. Data will be summarized by guadecitabine and each TC option within a given preselected TC option.

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 (or CxD1 visits completed for subjects randomized to BSC), dose cycles delayed, and dose reduced cycles will be summarized by treatment group and will be based on dose administrations, dose reductions, and dose delays identified by the study site and collected on the study drug administration CRFs. Delayed cycles will be identified and reported by the study site. For LDAC, MEC, and FLAG, dose-reduced cycles will be identified and reported by the study site while for the guadecitabine, azacitidine, decitabine, and HiDAC treatment groups, a dose-reduced cycle will be defined as a cycle in which:

- the planned dose for cycles ≥2 is less than planned dose for Cycle 1, OR
- the actual total dose (mg) for any day in the cycle is ≥25% reduction from planned dose (mg) calculated from BSA and planned dose (mg/m^2), OR
- the number of days of dosing in cycle is less than expected.

Summaries of delayed cycles and dose reduced cycles will be provided at both subject and cycle levels.

Dose intensity, presented as the incidence of subjects receiving <80% of their intended dose, will be summarized by cycle for the guadecitabine treatment group. Dose intensity will be calculated as the actual total dose divided by planned total dose for each treatment cycle.

Both completed or partially completed dose cycles are counted in these summaries. For BSC, cumulative dose, delayed cycles, dose-reduced cycles, and dose intensity will not be summarized.

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 (or the C1D1 visit date for subjects randomized to BSC) until 30 days after the last dose of study treatment (or until the Safety Follow-up visit date for subjects randomized to BSC), 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 after the Safety Follow-up visit date for subjects randomized to BSC), 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 dates will be imputed conservatively.

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 resulting in permanent treatment discontinuation, AE resulting in drug interruption, AE resulting in dose reduction, any serious AE (SAE), and subcategories of SAEs (fatal and non-fatal) 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 by decreasing frequency within each SOC. The number and percentage of subjects experiencing AEs will also be summarized by PT and sorted by event frequency. Related AEs, AEs Grade ≥3, related AEs Grade ≥3, serious AEs, related serious AEs, AEs with an outcome of death, AEs resulting in permanent treatment discontinuation, AEs resulting in drug interruption, and AEs resulting in dose reduction will be summarized similarly. In addition, AEs, related AEs, and SAEs will be summarized by SOC, PT, and CTCAE grade where subjects with multiple occurrences of the same AE will be counted once with its worst CTCAE grade.

7.4.3 30- and 60-Day All-cause Mortality

The 30- and 60-day all-cause mortality will be calculated as the proportions of subjects who have died within 30 or 60 days of study treatment initiation based on each subject's date of death relative to C1D1 (ie, date of death minus date of C1D1). Subjects who die 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.

In addition, a summary of all deaths, by cause of death (AE, progressive disease, other) and treatment group will be provided for the Efficacy Analysis Set (all randomized subjects)

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 (or the C1D1 visit date for subjects randomized to BSC), or those with a start date before C1D1 and a stop date on or after C1D1. Medications taken beyond 30 days from the last dose of study treatment (or after the Safety Follow-up visit date for subjects randomized to BSC), 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.

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 (including G-CSF, GM-CSF and ESAs), anti-infective medications (including but not limited to anti-bacterials, anti-mycotics, anti-mycobacterials, anti-virals, and immunoglobulins), and hydroxyurea given to reduce high counts during study treatment and not as part of a subsequent anti-leukemia treatment. These concomitant medications will be tabulated separately. Transfusions will be described separately as part of the efficacy analyses (Section 7.3.2.4).

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 study's Analysis Data Model (ADaM) specifications.

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 (Kratz et al 2012). 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.

Summaries will also be provided of the incidence of all new or worsening laboratory abnormalities (any CTCAE grade) and new or worsening CTCAE Grade ≥3 laboratory abnormalities by

parameter. A listing of potential Hy's Law cases will be provided. In addition, for selected laboratory parameters, a figure of mean values by visit will be generated.

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:

- Heart rate ≥110 bpm.
- Heart 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 at the safety follow-up visit), the mean of the available triplicate electrocardiogram values is entered in the CRF. For the ECG parameters (heart rate, PR interval, QRS duration, QT interval, and QTcF), the value and respective changes from baseline will be summarized by visit using mean, standard deviation, median, minimum, and maximum. Summaries will also be provided of the maximum post-baseline absolute QTcF and the maximum post-baseline increase in QTcF.

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

Relevant physical examination data may be presented in a data listing.

[redacted]

[redacted]

7.7 Interim Analyses and Data Monitoring

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

An interim futility analysis was conducted by the DMC at approximately one-third of the required 315 events, guided by the O'Brien-Fleming "lower boundary" that rules out the minimally important difference (hazard ratio of approximately 0.80). Based on the results of the interim futility analyses, the DMC recommended that enrollment in Study SGI-110-06 should be discontinued based on futility.

7.8 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.

7.9 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.

Protocol deviations related to the COVID-19 pandemic will be noted in the system and an additional summary table of important protocol deviations related to COVID-19 will be generated.

8.0 REFERENCES

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