16.1.1 Protocol and Protocol Amendments

Protocol Amendment 4.0 Global (29 October 2018)

- Summary of Changes – Amendment 4.0 Global (29 October 2018)
- Summary of Changes – Amendment 3.0 Global (14 February 2018)
- Summary of Changes – Amendment 2.0 Global (29 November 2017)
- Summary of Changes – Amendment 1.3 Hungary (24 May 2017)
- Summary of Changes – Amendment 1.2 UK (18 April 2017)
- Summary of Changes – Amendment 1.1 France (22 March 2017)

Clinical Study Protocol — SGI-110-06

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

PROTOCOL TITLE PAGE

Sponsor:	Astex Pharmaceuticals, Inc. 4420 Rosewood Drive, Suite 200 Pleasanton, CA 94588
Medical Monitor:	[redacted]
Drug Safety:	[redacted]
IND Number:	102743
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SPONSOR AND INVESTIGATOR SIGNATURE PAGE

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Study Acknowledgement

SGI-110-06: A Phase 3, Multicenter, Randomized, Open-Label Study of Guadecitabine (SGI-110) versus Treatment Choice in Adults with Previously Treated Acute Myeloid Leukemia

Version 4.0 (Amendment 4.0, Global), 29 October 2018

This protocol has been approved by Astex Pharmaceuticals, Inc. The following signature documents this approval.

Medical Monitor
[redacted]

[redacted]

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. Further, I agree to conduct this study in accordance with Good Clinical Practice and applicable regulatory requirements.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Astex Pharmaceuticals, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (printed)	Signature
Date	Study Center Number
Institution Name	Center Location: City, State or Province, Country

Please forward the original signed Protocol Acceptance Statement to Astex Pharmaceuticals, Inc.
Retain a copy of this form with the study protocol in your regulatory file.

PROTOCOL APPROVAL PAGE

SGI-110-06: A Phase 3, Multicenter, Randomized, Open-Label Study of Guadecitabine (SGI-110) versus Treatment Choice in Adults with Previously Treated Acute Myeloid Leukemia

Version 4.0 (Amendment 4.0 Global), 29 October 2018

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PROTOCOL APPROVAL PAGE

SGI-110-06: A Phase 3, Multicenter, Randomized, Open-Label Study of Guadecitabine (SGI-110) versus Treatment Choice in Adults with Previously Treated Acute Myeloid Leukemia

Version 4.0 (Amendment 4.0, Global), 29 October 2018

QA APPROVAL

Quality Assurance and Compliance

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APPROVED BY

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PROTOCOL SYNOPSIS

Study Number and Title:

SGI-110-06: A Phase 3, Multicenter, Randomized, Open-Label Study of Guadecitabine (SGI-110) versus Treatment Choice in Adults with Previously Treated Acute Myeloid Leukemia

Investigational Drug: Guadecitabine (SGI-110) for subcutaneous (SC) injection

Clinical Phase: 3

Study Centers Planned/Country: Multicenter global study (approximately 100 centers in 20 countries)

Study Objectives:

Primary Objective

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

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]

Study Design and Investigational Plan:

Multicenter, randomized, open-label, parallel-group study of guadecitabine vs TC. Approximately 404 subjects will be randomly assigned to either guadecitabine or TC in a 1:1 ratio. (Enrollment was stopped early; see below.)

Before randomization, the investigator will assign 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, granulocyte colony stimulating factor [G-CSF], +/- idarubicin [FLAG/FLAG-Ida]).
- Low intensity (low dose cytarabine [LDAC], decitabine, or azacitidine).
- Best Supportive Care (BSC).

All subjects in the TC arm may also receive hydroxyurea to control proliferative disease. Subjects in the guadecitabine arm may receive hydroxyurea in the first 30 days of treatment to control proliferative disease and allow a second cycle of guadecitabine. Subjects in the guadecitabine arm may receive guadecitabine earlier than the standard 28-day cycle to control proliferative disease. Subjects with disease progression leading to study therapy discontinuation may receive any other alternative anti-leukemia therapy; however, subjects in the TC arm are not allowed to cross over to guadecitabine. Data will be reviewed by an independent Data Monitoring Committee (DMC) at regular intervals primarily to evaluate safety during study conduct. Randomization will be stratified by intensity of preselected TC option (high intensity vs low intensity vs BSC), performance status (0-1 vs 2), baseline cytogenetics (poor risk vs other), and study center region (North America vs rest of world [ROW]).

Based on data from 278 randomly assigned subjects, the DMC recommended to stop further enrollment into the trial based on futility analysis that showed the trial is unlikely to show superiority of guadecitabine over TC for OS. Consequently, the study was closed to further enrollment in September 2018 (Amendment 4).

Study Population:
Approximately 404 adults with previously treated AML. (Enrollment was stopped with approximately 300 subjects randomly assigned to treatment [Amendment 4].)

Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria.

1. Adult subjects ≥18 years of age who are able to understand study procedures, comply with them, and provide written informed consent before any study-specific procedure.
2. History of cytologically or histologically confirmed diagnosis of AML (except acute promyelocytic leukemia) according to the 2008 World Health Organization (WHO) classification (bone marrow [BM] or peripheral blood [PB] blast counts ≥20%).
3. Performance status (Eastern Cooperative Oncology Group; ECOG) of 0-2.
4. Subjects with AML previously treated with induction therapy using an intensive chemotherapy regimen, defined as a regimen including cytarabine and an anthracycline, and who are refractory to induction (primary refractory) or in relapse after such induction with or without prior HCT.
5. Subjects must have either PB or BM blasts ≥5% at time of randomization.
6. Creatinine clearance or glomerular filtration rate ≥30 mL/min as estimated by the Cockroft-Gault (C-G) or other medically acceptable formulas, such as MDRD (Modification of Diet in Renal Disease) or CKD-EPI (the Chronic Kidney Disease Epidemiology Collaboration).
7. Women of child-bearing potential (according to recommendations of the Clinical Trial Facilitation Group [CTFG]; see protocol for details) must not be pregnant or breastfeeding and must have a negative pregnancy test at screening. Women of child-bearing potential and men with female partners of child-bearing potential must agree to practice 2 highly effective contraceptive measures of birth control (as described in the protocol) and must agree not to become pregnant or father a child (a) while receiving treatment with guadecitabine, decitabine, or azacitidine and for at least 3 months after completing treatment and (b) while receiving treatment with high-intensity TC or LDAC and for at least 6 months after completing treatment.

Exclusion Criteria

Subjects meeting any of the following exclusion criteria will be excluded from the study:

1. Known clinically active central nervous system (CNS) or extramedullary AML, except leukemia cutis.
2. Subjects who are in first relapse after initial induction, if they had a response duration of >12 months from date when first response was documented or if they are good candidates for HCT.
3. BCR-ABL-positive leukemia (chronic myelogenous leukemia in blast crisis).
4. Second malignancy currently requiring active therapy, except breast or prostate cancer stable on or responding to endocrine therapy.
5. Grade 3 or higher Graft Versus Host Disease (GVHD), or GVHD on either a calcineurin inhibitor or prednisone more than 5 mg/day. (Note: Prednisone at any dose for other indications is allowed.)
6. Prior treatment with guadecitabine for any indication, or more than 2 cycles of prior decitabine or azacitidine.
7. Hypersensitivity to decitabine, guadecitabine, or any of their excipients.
8. Treated with any investigational therapy within 2 weeks of the first dose of study treatment.
9. Total serum bilirubin >2.5 × upper limit of normal (ULN; except for subjects with Gilbert's Syndrome for whom direct bilirubin is <2.5 × ULN), or liver cirrhosis, or chronic liver disease Child-Pugh Class B or C.
10. Known active human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infection. Inactive hepatitis carrier status or low viral hepatitis titer on antivirals is allowed.
11. Known significant mental illness or other condition such as active alcohol or other substance abuse or addiction that, in the opinion of the investigator, predisposes the subject to high risk of noncompliance with the protocol.
12. Refractory congestive heart failure unresponsive to medical treatment; active infection resistant to all antibiotics; or non-AML-associated pulmonary disease requiring >2 liters per minute (LPM) oxygen, or any other condition that puts the subject at an imminent risk of death.
13. Subjects with high PB blasts >50% AND poor ECOG PS of 2.

Study Treatment:

Guadecitabine: 60 mg/m^2 SC daily on Days 1-5 and Days 8-12 or on Days 1-10 (first cycle).

Second cycle will be 60 mg/m^2 for either 10 days (Days 1-5 and 8-12 or Days 1-10) or 5 days (Days 1-5 only) based on assessment of disease response, and hematological recovery by Day ≥28 using the following general guidelines:

- Evidence of active leukemia in PB: no need for BM assessment, give second cycle with 10-day regimen with no delay.
- No evidence of active leukemia in PB: perform BM assessment and decide on course of action as follows:
  - BM blasts ≥5%: give second cycle with the 10-day regimen with no delay.
  - BM blasts <5%: assess recovery of PB normal counts as follows:
    - Absolute Neutrophil Count (ANC) >500/µL ***and*** platelets >50,000/µL: give second cycle with no delay using the 5-day regimen.
    - ANC <500/µL ***or*** platelets <50,000/µL: Delay treatment and repeat PB at least weekly and give second cycle either as a 5-day regimen (if both counts recover to a higher level than the limit above with no PB blasts); or 10-day regimen (appearance of evidence of active leukemia with PB blasts regardless of normal count recovery).

For Cycles ≥3, guadecitabine will be given for 5 days only (60 mg/m^2/day, Days 1-5). These guidelines may be modified if it is believed to be in the best interest of the subject according to the treating physician's best clinical judgment. Treatment should be given for at least 6 total 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.

Treatment Choice (TC): Before randomization, the investigator will assign each subject to one of the following TC options. The following doses and schedules are recommended based on prior published reviews and studies (Döhner et al 2015; Roboz et al 2014); however, small variations of dose, schedule, route, duration of treatment, and dose adjustment guidelines are allowed as long as they follow the locally approved prescribing information or institutional standard practice and are documented in the eCRF. TC options include:

- High intensity:
  - Intermediate or high dose cytarabine (HiDAC), recommended as 1-1.5 g/m^2 every 12 hours or up to 6 g/m^2/day for ≤6 days, maximum 36 g/m^2 per cycle.
  - Mitoxantrone, etoposide, and cytarabine (MEC): For example: mitoxantrone 6-12 mg/m^2 IV (recommended 8 mg/m^2), etoposide 80-200 mg/m^2 IV (recommended 100 mg/m^2), and cytarabine 1000 mg/m^2 IV; each daily for 5 days (Days 1-5).
  - Fludarabine, cytarabine, G-CSF, +/- idarubicin (FLAG/FLAG-Ida): For example: fludarabine 25-30 mg/m^2 IV daily Days 1-5; cytarabine 1-2 g/m^2 IV daily for up to 5 days (recommended to be given for 4 hours after fludarabine); G-CSF SC daily from Day 6 up to white cell count recovery with or without idarubicin 8 mg/m^2 IV daily on Days 3 to 5.
- Low intensity:
  - Low dose cytarabine (LDAC), 20 mg SC or IV twice daily on Days 1-10.
  - Decitabine 20 mg/m^2 IV daily on Days 1-5.
  - Azacitidine 75 mg/m^2 IV or SC daily on Days 1-7.
- BSC only.

Examples of variations in the above regimens include dose reductions in older subjects (>60 years) or subjects with prior HCT for the high intensity regimens; administering FLAG with no G-CSF; small variations in dose and days of treatment in the cycle; and giving azacitidine as a 5-2-2 schedule instead of 7 consecutive days.

Supportive care will be allowed in all study arms according to institutional standard practice. During treatment cycles of guadecitabine 10-day regimen and all high intensity regimens in the TC arm, prophylactic broad spectrum antibiotics and prophylactic broad spectrum antifungal treatment, with activity against *Aspergillus* species, such as posaconazole and voriconazole are highly recommended.

Hydroxyurea administration prior to randomization to control high counts is allowed. After randomization, subjects in the TC control arms may receive hydroxyurea to control proliferative disease as part of study treatment, while subjects in the guadecitabine arm may receive hydroxyurea in the first 30 days of treatment. In the guadecitabine arm, earlier treatment cycles (prior to Day 29) are allowed to control high proliferative counts.

Study Endpoints:

Primary Endpoint

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

Secondary Endpoints

- EFS defined as the number of days from randomization to the earliest of disease progression, treatment discontinuation, start of alternative anti-leukemia therapy (except 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 without red blood cell (RBC) or platelet transfusion for any period of 8 weeks after treatment.
- CR and CRh rates based on modified International Working Group (IWG) 2003 AML Response Criteria.
- 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 [EQ VAS]).
- Incidence and severity of adverse events (AEs).
- 30- and 60-day all-cause early mortality.

Study Assessments and Procedures:

A 14-day screening period is allowed (unless otherwise specified). After randomization, treatment cycles are intended to be repeated every 28 days. However, treatment delays are permitted to allow normal count hematological recovery in the absence of PB blasts, particularly with more intensive treatment such as guadecitabine 10-day regimen, HiDAC, MEC, and FLAG/Ida. Visits will occur on treatment days, as necessary. In addition, during the first 3 cycles, visits will occur weekly on Days 8, 15, and 22, then on Day 15 in Cycles 4-6. In Cycles >6, visits will only occur on treatment days (if necessary), with study-specified assessments on Day 1. Additional visits based on treatment effect and blood counts may be done at the investigator's discretion. Subjects will attend a safety follow-up visit after the last study treatment. For subjects who discontinue study treatment before Cycle 6, long term follow-up visits will occur monthly until 6 months after the start of study treatment and then every 3 months thereafter. For subjects who discontinue study treatment after Cycle 6, long-term follow-up visits will be every 3 months.

Efficacy Assessments:

Survival will be monitored and documented throughout the study. Transfusion requirements (RBC and platelets) will be recorded every month in the first 6 months then at every study visit until disease progression. All hospital admissions will be recorded and used to determine NDAOH every month in the first 6 months then at every study visit until disease progression. Clinical response is based on both PB sampling and BM aspirate or biopsy assessments. In cycles where a BM sample is not collected, the most recent previous BM sample will be used for response assessment.

Peripheral blood will be assessed at baseline and at specified time points in each cycle. Bone marrow aspirate or biopsy (with touch prep slides) will be performed at screening and then at the end of Cycles 1, 3, and 6, unless PB shows persistence of ≥5% leukemic blasts that excludes the possibility of a marrow response. After Cycle 6, BM assessment, BM aspirate, or biopsy (with touch prep slides) 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. BM may be done more frequently or at additional time points at the discretion of the treating physician. Response evaluation may be done centrally by an independent blinded central reviewer based on BM assessment and PB counts. In subjects who undergo HCT, time to stem cell engraftment will be calculated from the day of transplant to the first day of 3 consecutive days of PB ANC of >500/μL.

[redacted]

[redacted]

Health-related QOL Assessment:
EQ-5D 5 level (EQ-5D-5L and EQ-VAS) will be administered before treatment on Day 1 of each cycle for 6 cycles then at every study visit until disease progression. For subjects who discontinue study treatment before Cycle 6 it will be administered monthly until 6 months after the start of study treatment, then at every study visit until disease progression.

Safety Assessments:
Documented safety assessments will include AEs, concomitant medications, physical examination findings, vital signs, electrocardiogram (ECG) measurements, ECOG performance status, and clinical laboratory parameters (hematology and chemistry), according to the schedule of events.

Sample Size and Statistical Analyses:

Sample Size Calculation:
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 enrolment will be non-uniform over an 18-month period (with additional follow-up of 8 months) during which 3 to 29 subjects per month are expected to be enrolled in the first 10 months in increasing order followed by 30 subjects per month in months 11-18, then approximately 404 subjects need to be randomized. If, after a follow-up of 12 months from the last subject randomized, the 315 death events have not occurred, the primary analysis will be conducted at 12 months from the last subject randomized (if 277 or more death events have occurred) or after at least 277 death events have been observed (corresponding to 86% power). Based on DMC recommendation to stop further enrollment, the time of primary analyses is 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.

Efficacy:
The primary endpoint of OS will be displayed using a Kaplan-Meier estimate and will be compared between the 2 treatment groups using a log-rank test stratified by the randomization stratification factors with an overall 2-sided alpha level of 0.05. In order to control the type I error at an overall 0.05 level (2-sided), the nominal alpha to be used in the final analysis will be calculated accounting for the alpha already spent at the interim analysis. If statistical significance is achieved for OS, hierarchically EFS, survival rate at 1-year, NDAOH, transfusion independence rate, combined CR+CRh rate, CRc rate, and HCT rate will be analyzed. Rates of transfusion independence, CR, CRh, combined CR+CRh, CRc, and HCT will be compared between the 2 treatment groups using a Cochran Mantel-Haenszel test. EFS will be analyzed using the same method as used for the OS analysis. One-year survival rate will be tested using Kaplan-Meier estimates, and standard errors estimated by the Greenwood formula. NDAOH will be evaluated using an analysis of variance model.

Safety:
Safety will be assessed by subject-reported and investigator-observed AEs and 30- and 60-day all-cause mortality, along with physical examination, laboratory tests (hematology and chemistry), vital signs, and ECGs. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) with severity categorization based on Common Terminology Criteria for Adverse Events (CTCAE) v4.03. Treatment exposure, AEs including relatedness and severity, serious AEs (SAEs), and reasons for treatment discontinuation will be tabulated and presented for all subjects who receive any amount of study treatment. Concomitant medication will be coded using WHO Drug Dictionary. Thirty (30) and 60-day mortality rates will be calculated as number of deaths, regardless of cause, within 30 or 60 days from the first study dose (C1D1) divided by the total number of subjects included in the safety dataset.

Interim Analysis:
One interim analysis of OS is planned with maximum spendable 2-sided alpha of 0.01, using the Lan-DeMets implementation of an O'Brien Fleming boundary adjusted by the actual proportion of events at the interim relative to the target final 315 death events. The interim analysis was to be conducted by an independent DMC after approximately half of the required death events have occurred. However, after approximately one-third of the required 315 death events had occurred, the DMC recommended to discontinue enrollment based on futility, so no further interim analysis will be conducted. The DMC will also perform regular data reviews with the main purpose of ensuring safety of study subjects and quality of trial conduct.

Study Duration: The expected study duration is approximately 26 months including 18 months for completing enrollment and approximately 8 months follow-up before the primary analyses. The study started in Q1 2017. Based on DMC recommendation after futility analyses, enrolment was stopped in September 2018. Follow-up for the primary analyses will be stopped in Q3 2019 or when the last subject is off study.
Compliance Statement: The study will be conducted in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, US Title 21 CFR Parts 11, 50, 54, 56, and 312; the EU Clinical Trials Directive and its successor; principles enunciated in the Declaration of Helsinki; and all human clinical research regulations in countries where the study is conducted.

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ABBREVIATIONS AND DEFINITIONS

AE	adverse event
ALT	alanine transaminase (serum glutamic pyruvic transaminase [SGPT])
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
AUC	area under the curve
BCR-ABL	chronic myelogenous leukemia in blast crisis
BED	biologically effective dose
BM	bone marrow
BSA	body surface area
BSC	best supportive care
CBC	complete blood count
CDA	cytidine deaminase
CFR	Code of Federal Regulations
C-G	Cockcroft-Gault
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum concentration
CMML	chronic myelomonocytic leukemia
CNS	central nervous system
CR	complete response
CRc	composite complete response (CRc=CR+CRi+CRp)
CRh	complete response with partial hematologic recovery
CRi	CR with incomplete blood count recovery
CRp	CR with incomplete platelet recovery
CRF/eCRF	case report form/electronic case report form
CTCAE	Common Terminology Criteria for Adverse Events
DLI	donor lymphocytes infusion
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EMEA	European Agency for the Evaluation of Medicinal Products
EQ VAS	EuroQOL Visual Analogue Scale
EU	European Union
FAB	French-American-British
FDA	Food and Drug Administration
FIH	first in human
FLAG	fludarabine, cytarabine, and G-CSF
FLAG-Ida	fludarabine, cytarabine, G-CSF and idarubicin
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factors
GLP	Good Laboratory Practice
GVHD	graft versus host disease
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HCT	hematopoietic cell transplant
HI	hematological improvement

HiDAC	high dose cytarabine
HIV	human immunodeficiency virus
HMA	hypomethylating agent
HNSTD	highest non-severely toxic dose
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product (guadecitabine)
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
IWG	International Working Group
LDAC	low dose cytarabine
LINE-1	long interspersed nucleotide element-1
LPM	liters per minute
mCR	marrow complete response
MDRD	Modification of Diet in Renal Disease
MDS	myelodysplastic syndrome
MEC	mitoxantrone, etoposide and cytarabine
MedDRA	Medical Dictionary for Regulatory Activities
MSDS	Material Safety Data Sheet
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NDAOH	number of days alive and out of hospital
NOAEL	no observed adverse effect level
OSHA	Occupational Safety and Health Administration
OS	overall survival
PB	peripheral blood
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PR	partial response
PT	preferred term
QOL	quality of life
RBC	red blood cells
ROW	rest of world
r/r	relapsed/refractory
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SE	standard error
SGI-110	guadecitabine
SOC	System Organ Class
SSC	Study Steering Committee
STD_{10}	severely toxic dose causing mortality in 10% of animals
SUSAR	serious unexpected suspected adverse reaction
TC	treatment choice
TK	toxicokinetic
TN	treatment naive
ULN	upper limit of normal
VAS	visual analog scale

WBC	white blood cell
WHO	World Health Organization

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, US Title 21 Code of Federal Regulations (CFR) Parts 11, 50, 54, 56, and 312; the European Union (EU) Clinical Trials Directive and its successor; principles enunciated in the Declaration of Helsinki; and all human clinical research regulations in countries where the study is conducted (see Section 13.0).

1.0 INTRODUCTION AND BACKGROUND

1.1 Background of the Disease

Acute myeloid leukemia (AML) is the most common acute leukemia diagnosed in adults. In the United States, the American Cancer Society estimated that 19,950 new cases of AML will be diagnosed in 2016 and approximately 10,430 will die from their disease. The average age of a patient with AML is about 67 years; AML is generally a disease of older people and is uncommon before age 45 (American Cancer Society 2016). As the population in the United States ages, there appears to be an increasing incidence of AML (National Cancer Institute 2016).

Characteristically AML is a disease associated with termination in cellular differentiation and uncontrolled proliferation of clonal immature myeloid precursors (myeloblasts) in the bone marrow and blood (Scheinberg et al 2001). AML is differentiated from other hematopoietic malignancies by the presence of greater than 20% myeloblasts in the bone marrow or blood. AML can be divided into de novo and secondary disease (Scheinberg et al 2001; Appelbaum et al 2001). Patients presenting with de novo AML often do not have any identifiable risk factor. Secondary causes for AML range from previous myelodysplastic syndrome (MDS), Down syndrome, Fanconi anemia, ataxia-telangiectasia, long-term treatment consequences of certain chemotherapeutic agents, therapeutic or environmental radiation, and exposure to environmental hazards (eg, benzene). The common feature of all AML is genetic mutation, which in 70% of patients results in visible cytogenetic abnormalities when the leukemia cells are karyotyped.

In AML, myeloblasts crowd out normal hematopoietic cells in the bone marrow, leaving the patient with insufficient erythrocytes, platelets, and neutrophils. The consequent pancytopenias cause 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.

AML is diagnosed and classified according to the World Health Organisation (WHO) classification, which considers the genetic, immunophenotypic, biological, and clinical characteristics of the disease (Vardiman et al 2009). The WHO classification usually supersedes the previously used French-American-British (FAB) classification of AML, which was developed based on the morphological and cytological characteristics of the disease (Meenaghan et al 2012).

1.2 Treatment Options

Traditional, standard therapy consists of 2 phases: induction therapy followed by consolidation or intensification therapy (Estey and Döhner 2006). The initial goal in treating AML is to produce complete remission with induction chemotherapy. This is followed by consolidation or intensification therapy with additional chemotherapy (high-dose cytosine arabinoside or other combination regimens) or hematopoietic cell transplant (HCT) with the ultimate goal of cure. The standard intensive induction chemotherapy has been the same for decades and mainly comprises 7 days of Ara-C and 3 days of an anthracycline (daunorubicin or idarubicin), known as the 7+3 regimen, which produces remission in 70% to 80% of patients for whom the treatment is appropriate (Tefferi and Letendre 2012).

Patients who do not enter remission after 1-2 cycles of this treatment are considered refractory. Remission is defined as normal cellularity of the bone marrow, with blast levels of less than 5%, and morphologically normal hematopoiesis with a neutrophil count over 1000/µL and a platelet count over 100,000/µL (National Comprehensive Cancer Network [NCCN] AML Guidelines 2014).

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, leading to an overall median survival of approximately 9 months from diagnosis (Löwenberg et al 1989; Goldstone et al 2001; Wahlin et al 2001; Ross et al 2015). These figures have not improved within the last 3 decades (Roboz 2011; Stalfelt 1994; Alibhai et al 2007).

The incidence of AML increases with age, with more than 50% of patients with AML being over 65 years of age (Medeiros 2015). For these older patients, traditional chemotherapy provides minimal chance for durable remission, as well as significant toxicity, because of patients' increased risk factors and inability to cope with aggressive treatment (Kuendgen and Germing 2009). Induction mortality has been reported to be as high as 20% (Marks 2012).

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). Treatment strategy is directed towards getting the patient into remission and then to transplant. Otherwise, palliation is the goal. Patients whose first remission lasted longer than one year have a good chance at achieving a second remission with standard induction therapy and, if the transplant is successful, do almost as well as patients transplanted in first remission (Ossenkoppele et al 2016). 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. Safe and effective treatments prolonging survival and/or bridging to transplant are urgently needed for patients with relapsed or refractory (r/r) AML.

Choice of treatment for patients with r/r AML is based mostly on evidence from small studies and considers factors such as age, performance status, previous treatment history and responses, cytogenetics, access to care, and availability of medications (Roboz et al 2014). 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), such as mitoxantrone, etoposide, and cytarabine (MEC) (Archimbaud et al 1991; Archimbaud et al 1995) and fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin (FLAG-Ida). The hypomethylating agents (HMAs) decitabine and azacitidine, though mostly studied in 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

The DNA methylation inhibitors azacitidine and decitabine (also known as HMAs), are approved in several jurisdictions for treatment of intermediate and high risk patients with MDS including chronic myelomonocytic leukemia (CMML). 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). Guadecitabine is cleaved by intra- and extracellular phosphorylases and other enzymes, releasing decitabine. This cleavage in vivo (in primates) results in gradual release of decitabine both extra- and intracellularly, thus prolonging decitabine half-life and effective exposure to decitabine.

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.

Guadecitabine is being evaluated in subjects with hematological malignancies (MDS and AML) and solid tumors (ovarian cancer, hepatocellular carcinoma [HCC]). Long interspersed nucleotide element-1 (LINE-1) demethylation was demonstrated in AML/MDS subjects treated with guadecitabine (Issa et al 2015). Clinical responses in subjects with AML and MDS have been observed in the Phase 1-2 study (SGI-110-01) (Issa et al 2015; Kantarjian et al 2013).

A Phase 3 study (SGI-110-04) of guadecitabine versus treatment choice (TC) is currently ongoing in adults with previously untreated AML who are unfit to receive or who are not considered candidates for intensive induction chemotherapy. Another Phase 3 study (SGI-110-07) of guadecitabine versus TC is planned for adults with MDS or CMML who failed or relapsed after prior treatment with azacitidine, decitabine, or both.

[redacted]

[redacted]

1.5 Summary of Clinical Data for Guadecitabine

Guadecitabine has been evaluated in patients with hematological malignancies (MDS and AML) and in patients with solid tumors (ovarian cancer and HCC). LINE-1 demethylation, gene-specific demethylation, and clinical responses have been observed in patients with AML and MDS (Study SGI-110-01), as well as in patients with ovarian cancer and HCC (Studies SGI-110-02 and SGI-110-03).

The results from the Phase 1 dose escalation of Study SGI-110-01 and Phase 2 dose expansion of Study SGI-110-01 in patients with relapsed or refractory AML (r/r AML) have been summarized below. Please refer to the most recent IB for summaries of the other clinical studies.

1.5.1 Phase 1-2 Dose Escalation and Dose Expansion Study (Study SGI-110-01)

Study SGI-110-01 was a first-in-human (FIH), multicenter, randomized study in patients with MDS or AML. It was conducted in 2 phases and enrolled 401 subjects. Phase 1 is complete and Phase 2 is ongoing.

- Phase 1 Dose Escalation: 93 subjects with refractory or relapsed MDS or AML treated with guadecitabine.
- Phase 2 Dose Expansion: 308 subjects with MDS or AML treated with guadecitabine.

All treatment cycles were 28-day cycles in the Phase 1-2 study.

1.5.1.1 Phase 1 Dose Escalation (Study SGI-110-01)

Phase 1 dose escalation was performed in subjects with refractory or relapsed MDS or AML (Issa et al 2015) who had Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and acceptable liver and kidney function. Co-primary endpoints were maximum tolerated dose (MTD) and biologically effective dose (BED).

Subjects were treated with 3 different dosing schedules (Daily×5, Once Weekly for 3 weeks, and Twice Weekly for 3 weeks). Guadecitabine was given SC in 28-day cycles starting at a dose of 3 mg/m^2 once daily on Days 1-5 (Daily×5). Doses were escalated to 125 mg/m^2 using the Daily×5 schedule. The Once-Weekly (Days 1, 8, and 15) dosing schedule was initiated at 6 mg/m^2 and was escalated to 125 mg/m^2. An amendment added the Twice-Weekly (Days 1, 4, 8, 11, 15, 18) dosing schedule, which investigated guadecitabine at 60 and 90 mg/m^2.

The MTD was 90 mg/m^2/day using the Daily×5 schedule for MDS subjects. The MTD was not reached for subjects with AML who were dosed up to 125 mg/m^2/day Daily×5. Two subjects with MDS developed DLTs at the highest dose (125 mg/m^2/day) in the Daily×5 regimen. One subject had thrombocytopenia and neutropenia; the other subject had febrile neutropenia, thrombocytopenia, and fatal sepsis. The MTD was not reached for the once weekly (up to 125 mg/m^2/dose) or the twice weekly (up to 90 mg/m^2/dose) regimens.

Potent dose-related DNA demethylation occurred on the Daily×5 regimen. The BED (defined as the minimum dose that achieves maximal demethylation of LINE-1 from 3 successive cohorts) was 60 mg/m^2/day for the Daily×5 schedule. DNA methylation reached a plateau at 60 mg/m^2 and was similar at 60, 90, and 125 mg/m^2 Daily×5. Less demethylation was observed with the once weekly regimen; the twice weekly regimen did not lead to better LINE-1 demethylation than the Daily×5 regimen.

A total of 74 subjects with r/r AML were treated with guadecitabine in Phase 1 dose escalation. Responses were observed starting at 36 mg/m^2. Of 49 subjects treated at 36 mg/m^2 or higher in the daily and weekly regimens, 5 composite complete responses (CRc: complete response [CR] + complete response with incomplete blood count recovery [CRi] + complete response with incomplete platelet recovery [CRp]), including 2 CRs, were observed. A total of 19 subjects with relapsed/refractory MDS were treated in the Phase 1 study. Six subjects with MDS had clinical responses: 2 subjects had marrow complete response (mCR), and 4 had hematological improvement (HI; 3 subjects had single-lineage HI and 1 subject had bi-lineage HI).

The most common Grade 3 or higher adverse events (AEs) were febrile neutropenia (38/93; 41%), pneumonia (27/93; 29%), thrombocytopenia (23/93; 25%), anemia (23/93; 25%), and sepsis (16/93; 17%). The most common serious AEs (SAEs) were febrile neutropenia (29/93; 31%), pneumonia (26/93; 28%), and sepsis (16/93; 17%).

In summary, Phase 1 showed that the Daily×5 regimen induced maximal DNA demethylation, and the dose of 60 mg/m^2/day Daily×5 was the BED. The 90 mg/m^2/day Daily×5 regimen was the

highest well-tolerated dose for both MDS and AML subjects. Once weekly and twice weekly regimens were well tolerated at all doses, but did not improve biological or clinical activity relative to the Daily×5 regimen.

1.5.1.2 Phase 2 (SGI-110-01 Dose Expansion)

Phase 2 was a dose-expansion, dose-ranging trial and was opened as a multicenter, open-label, randomized comparison of 60 vs 90 mg/m^2 guadecitabine SC Daily×5 (once daily on Days 1-5). The 60 mg/m^2 Daily×5 dose was chosen because it represented the BED from Phase 1, while the 90 mg/m^2 dose was chosen to explore benefit from a higher dose that was still well tolerated in both MDS and AML subjects. Subjects were stratified by disease type (treatment-naïve elderly AML, relapsed/refractory AML, HMA treatment-naïve MDS, and relapsed/refractory MDS). A subsequent amendment, applying only to AML subjects allowed initial intensification with a 10-day regimen (dosing on Days 1-5 and 8-12) at 60 mg/m^2/day for up to 4 cycles, followed by continuation of treatment with the Daily×5 regimen. The 10-day regimen was studied first in r/r AML subjects and then in treatment-naïve elderly AML subjects.

Phase 2 in the cohort of subjects with r/r AML is complete and the results for these subjects are described below. Key eligibility for r/r AML subjects in Study SGI-110-01 Phase 2 included age ≥18 years, confirmed diagnosis of AML, in relapse or refractory following standard treatment, and ECOG performance status of 0-2.

There was no limit on the number of prior regimens, white blood cell (WBC) count, or bone marrow (BM) blasts count. Only 1 previous cycle of decitabine or azacitidine was allowed. Patients with acute promyelocytic leukemia (M3 classification) were excluded from the study.

Subjects were randomized to receive either 60 or 90 mg/m^2/day guadecitabine once daily on Days 1-5 of a 28-day cycle. An additional 10-day cohort was added; subjects in this cohort were treated with 60 mg/m^2/day guadecitabine once daily on Days 1-5 and Days 8-12 of a 28-day cycle for at least 2 cycles followed by the 5-day regimen in subsequent cycles. The primary endpoint for r/r AML subjects was CRc rate (CRc rate = CR + CRp + CRi).

A total of 108 subjects were enrolled with r/r AML in Phase 2, of whom 103 subjects received treatment. Fifty subjects were randomized and treated with the 5-day regimen (24 and 26 subjects received study treatment at 60 or 90 mg/m^2 Daily×5, respectively). Fifty-three subjects were enrolled and treated with guadecitabine 60 mg/m^2 in the 10-day regimen (according to protocol amendment 3, without randomization).

Table 1 presents demographic and baseline characteristics for subjects with r/r AML enrolled and treated in Phase 2 Dose Expansion. The median age of subjects was 60 years, 60% of subjects were male, and 81% were White. The 10-day group was nearly equally divided between the sexes (51% men) compared with the 5-day group (70% men), but all other demographic characteristics were similar across treatment groups. Most subjects (73%) had an ECOG status of 1 at baseline and had received a median of 2 prior regimens with up to 10 prior regimens including 11% with

prior HMA treatment. The median time since diagnosis was 261 days (range 8 to 3214 days). Of note are the poor prognostic features of subjects treated in this study (18% of subjects had prior HCT and 41% had poor risk cytogenetics).

Table 1: Summary of Demographic and Baseline Characteristics: Relapsed/Refractory AML Subjects (Phase 2, Study SGI-110-01)

Characteristic		5-Day 60 mg/m² (N=24)	5-Day 90 mg/m² (N=26)	5-Day Total (N=50)	10-Day 60 mg/m² (N=53)	10-Day Total (N=103)
Age, yr	Median	58.43	65.50	62.34	57.47	60.13
	Range	22.0-77.0	30.0-81.7	22.0-81.7	29.2-82.5	22.0-82.5
Gender (n, %)	Male	15 (63)	20 (77)	35 (70)	27 (51)	62 (60)
	Female	9 (38)	6 (23)	15 (30)	26 (49)	41 (40)
ECOG (n, %)	0	2 (8)	3 (12)	5 (10)	9 (17)	14 (14)
	1	20 (83)	20 (77)	40 (80)	35 (66)	75 (73)
	2	2 (8)	3 (12)	5 (10)	9 (17)	14 (14)
Time Since Diagnosis to C1D1 (Days)	Median	369.5	292.0	342.0	177.0	261.0
	Range	27-3198	8-1611	8-3198	17-3214	8-3214
BM Blasts (%)	Median	34.0	35.5	35.0	32.0	33.0
	Range	9-93	2-94	2-94	4-95	2-95
PB Blasts (%)	Median	5.0	14.0	10.0	2.5	6.0
	Range	0-95	0-81	0-95	0-99	0-99
WBC ($x10^9$/L)	Median	1.65	2.12	1.70	2.10	1.80
	Range	0.3-18.7	0.3-18.6	0.3-18.7	0.2-75.5	0.2-75.5
Cytogenetics (n, %) (Company Assessment)	n	24	26	50	53	103
	Better Risk	0	0	0	0	0
	Int Risk	12 (50)	14 (54)	26 (52)	26 (49)	52 (50)
	Poor Risk	9 (38)	11 (42)	20 (40)	22 (42)	42 (41)
	Not evaluable	3 (13)	1 (4)	4 (8)	5 (9)	9 (9)
Prior Decitabine or Azacitidine (n, %)		1 (4)	2 (8)	3 (6)	8 (15)	11 (11)
Prior HCT (n, %)		5 (21)	5 (19)	10 (20)	9 (17)	19 (18)
Number of Prior Regimens	Median	2.5	2.0	2.0	2.0	2.0
	Range	1-5	1-10	1-10	1-7	1-10
Time Since Last Anti-Leukemia Therapy (n, %)	n	24	26	50	53	103
	<6 Months	19 (79)	20 (77)	39 (78)	43 (81)	82 (80)
	≥6 Months	5 (21)	5 (19)	10 (20)	10 (19)	20 (19)
	Unknown	0	1 (4)	1 (2)	0	1 (<1)

AML=acute myelogenous leukemia; BM=bone marrow; C1D1=cycle 1 day 1; ECOG=Eastern Cooperative Oncology Group; HMA= hypomethylating agent; PB=peripheral blood; WBC=white blood cell.
Note 1: Only 2 subjects had more than 1 month prior HMA therapy.
Source: CSR SGI-110-01-B Table 14.2.1 and, for prior HCT, Appendices 16.2.9.1 and 16.2.11

Overall, 24 of 103 subjects with AML who were either refractory to prior treatment or relapsed after achieving a CR from induction therapy responded to treatment with guadecitabine (Table 2). The overall CRc rate was 23.3% (95% CI: 15.5-32.7). Of these 24 responders,

14 achieved a best response of CR, 6 achieved a best response of CRi, and 4 achieved a best response of CRp.

The CRc and CR rates of the 10-day regimen were approximately double that of the 5-day regimen (10-day CRc and CR rates, 30% and 19%, respectively; 5-day CRc and CR rates, 16% and 8%, respectively).

In the 5-day regimen, the CR and CRc rates were generally not different between 60 and 90 mg/m^2 (8.3% and 7.7% for CR, and 12.5% vs 19.2% for CRc for the 60 and 90 mg/m^2 dose groups, respectively).

Of the 24 responders, 5 had prior HCT and 8 had poor cytogenetic risk factors at baseline, and all responders who had evaluable LINE-1 data achieved at least -20% LINE-1 demethylation.

Table 2: Best Response in Subjects with r/r AML (Efficacy Data Set)

	Response Rate, n (%) [95% Confidence Interval (CI)]				
	5-Day			**10-Day**	
Response Category[a]	**60 mg/m² (N=24)**	**90 mg/m² (N=26)**	**Total (N=50)**	**60 mg/m² (N=53)**	**Total (N=103)**
Complete response (CR)	2 (8.3)	2 (7.7)	4 (8.0)	10 (18.9)	14 (13.6)
CR with incomplete blood count recovery (CRi)	1 (4.2)	3 (11.5)	4 (8.0)	2 (3.8)	6 (5.8)
CR with incomplete platelet recovery (CRp)	0	0	0	4 (7.5)	4 (3.9)
Partial response (PR)	0	0	0	0	0
Nonresponder (NR)	21 (87.5)	18 (69.2)	39 (78.0)	36 (67.9)	75 (72.8)
Not evaluable (NE)[b]	0	3 (11.5)	3 (6.0)	1 (1.9)	4 (3.9)
CRc rate (CR+CRi+CRp)	**3 (12.5) [2.7 - 32.4]**	**5 (19.2) [6.6 – 39.4]**	**8 (16.0) [7.2 – 29.1]**	**16 (30.2) [18.3 – 44.3]**	**24 (23.3) [15.5 – 32.7]**

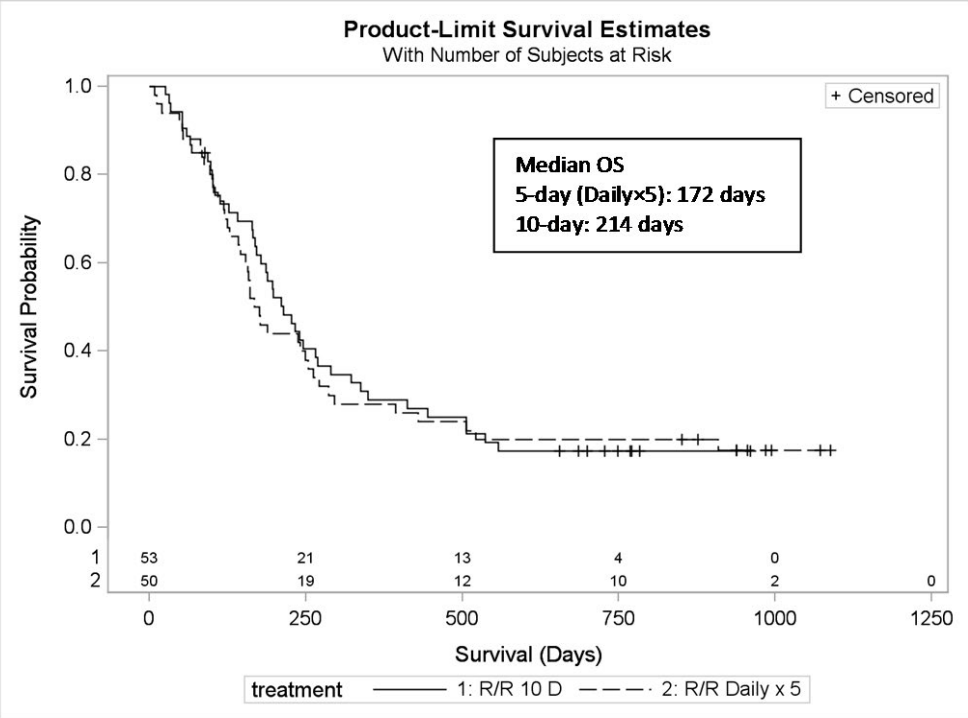
AML=acute myelogenous leukemia; CRc=composite complete response.
[a] Modified IWG 2003 AML Response Criteria (Cheson et al 2003).
[b] NE subjects are included in the denominator for response rate calculation.
Source: CSR SGI-110-01-B Table 14.3.1.1

Survival data were censored for 19 subjects. Of these 19 subjects, 18 were alive (2 still on treatment with guadecitabine) at the time of the data cut-off, and 1 withdrew consent. The overall median follow-up was 876 days (29.2 months [95% CI: 25, 32 months]). The median overall survival in r/r AML subjects was 197 days (6.6 months [95% CI: 164, 246 days]). Overall 1- and 2-year survival rates were 28% and 19%, respectively.

Figure 1 depicts survival estimates by dosing regimen (5-day and 10-day). Median follow-up was 956 days (31.9 months) for the 5-day regimen and 749 days (25.0 months) for the 10-day regimen. Median survival was 214 days (7.1 months) for subjects on the 10-day regimen and 172 days (5.7 months) for those on the 5-day regimen.

Survival was highly associated with response. Median OS could not be estimated for responders (subjects with CRc), and was 168 days (5.6 months) for nonresponders. The longer survival for CRc subjects was not dependent on whether or not they went into HCT following response.

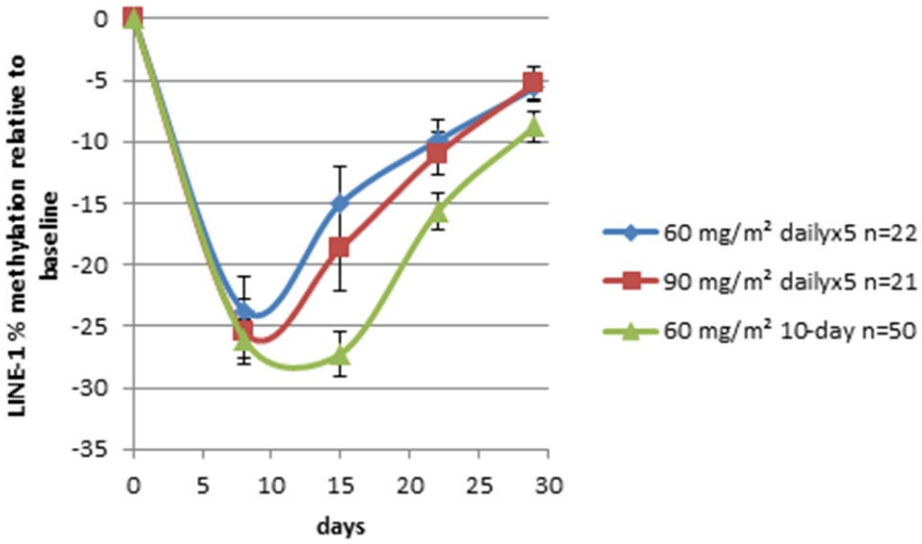
Figure 1: Product-Limit Survival Estimates in r/r AML Subjects by Regimen (5-Day and 10-Day)



OS=overall survival.
Source: CSR SGI-110-01-B Table 14.3.4.1 and Figure 14.3.4.4

Guadecitabine effects on global DNA methylation were measured by a quantitative bisulfite pyrosequencing method for LINE-1 methylation analysis as previously reported (Yang et al 2004). Ninety-three subjects with r/r AML provided sufficient samples at different time points to assess guadecitabine effects on LINE-1 methylation: 22 treated with 60 mg/m^2 on the 5-day regimen, 21 with 90 mg/m^2 on the 5-day regimen, and 50 with 60 mg/m^2 on the 10-day regimen. Figure 2 shows the kinetics of LINE-1 demethylation for these 3 groups of subjects. There was not a major difference in extent and duration of LINE-1 demethylation between subjects treated on the 5-day regimen at doses of 60 or 90 mg/m^2: the maximum mean (±SE) LINE-1 demethylation was -20.6% ± 2.8 for 60 mg/m^2 and -22.6% ± 2.8 for 90 mg/m^2. Both groups of subjects on the 5-day regimen re-methylated LINE-1 sequences with the same kinetics. Maximum LINE-1 demethylation was greater with the 10-day regimen (-30.6% ± 1.6) than with the 5-day regimen. Further, for the 10-day regimen, this decrease was sustained until Day 15.

Figure 2: Guadecitabine Average LINE-1 Demethylation by Dose and Treatment Schedule



Source: SGI-110-01-B CSR Table 14.5.1.1

The majority of subjects (n=80) showed a maximum LINE-1 % decrease from baseline ≥10%. Overall maximum LINE-1 demethylation was significantly higher (P=0.0002) in responders (-34.89% ±1.78, n=22) than in nonresponders (-23.85% ±1.53, n=69).

Table 3 presents AEs Grade ≥3 by preferred term (PT) with incidence of ≥10% in either the 5-day or 10-day regimens regardless of relationship to study treatment. Overall, the most common Grade ≥3 AEs were febrile neutropenia (60%); pneumonia and thrombocytopenia (36% each); and anemia (31%). AE incidence was generally higher for the 10-day regimen compared with the total 5-day regimen. Common AEs Grade ≥3 with an absolute difference in incidence ≥10% higher for the 10-day regimen compared with the 5-day regimen, respectively, include febrile neutropenia (66% vs 54%), pneumonia (45% vs 26%), thrombocytopenia (51% vs 20%), anemia (43% vs 18%), neutropenia (28% vs 10%), and sepsis (21% vs 10%).

Table 3: Adverse Events Grade ≥3 by Decreasing Incidence (≥10% of Total) in Subjects with r/r AML

	Number (%) of Subjects				
	5-Day			10-Day	
Adverse Event	60 mg/m² (N=24)	90 mg/m² (N=26)	Total (N=50)	60 mg/m² (N=53)	Total (N=103)
Any Event	20 (83)	25 (96)	45 (90)	50 (94)	95 (92)
- Febrile neutropenia	10 (42)	17 (65)	27 (54)	35 (66)	62 (60)
- Pneumonia	4 (17)	9 (35)	13 (26)	24 (45)	37 (36)
- Thrombocytopenia	5 (21)	5 (19)	10 (20)	27 (51)	37 (36)
- Anaemia	5 (21)	4 (15)	9 (18)	23 (43)	32 (31)
- Neutropenia	2 (8)	3 (12)	5 (10)	15 (28)	20 (19)
- Sepsis	3 (13)	2 (8)	5 (10)	11 (21)	16 (16)
- Hypokalaemia	5 (21)	3 (12)	8 (16)	6 (11)	14 (14)
- Bacteraemia	3 (13)	3 (12)	6 (12)	6 (11)	12 (12)
- Cellulitis	4 (17)	0	4 (8)	6 (11)	10 (10)
- Leukopenia	3 (13)	3 (12)	6 (12)	4 (8)	10 (10)

Source: SGI-110-01-B CSR Table 14.4.2.5.1

The 30- and 60-day all-cause mortality rates (Table 4 were similar across treatments. Early all-cause mortality was reported in 3.9% and 11.7% of subjects for 30-day and 60-day mortality, respectively, which is lower than what would be expected from intensive cytotoxic therapy. The consistently higher incidence of Grade ≥3 AEs reported with the 10-day regimen (Table 3) did not translate into higher early mortality, suggesting that the increase in toxicity was manageable in the context of a fatal disease such as r/r AML.

Table 4: 30-day and 60-day All-Cause Mortality Rates in Subjects with r/r AML

	Number (%) of Subjects				
	5-Day			10-Day	
Mortality	60 mg/m² (N=24)	90 mg/m² (N=26)	Total (N=50)	60 mg/m² (N=53)	Total (N=103)
30-day	2 (8.3)	1 (3.8)	3 (6.0)	1 (1.9)	4 (3.9)
60-day	4 (16.7)	2 (7.7)	6 (12.0)	6 (11.3)	12 (11.7)

Source: SGI-110-01-B CSR Table 14.4.3.1

Based on these results for r/r AML, we conclude that the recommended regimen comprises the previously identified BED of 60 mg/m^2/day for 5 days (Days 1-5), with initial intensification (first 1-2 cycles) with 10-day dosing (Days 1-5 and 8-12). This regimen, including the initial intensification, appears to facilitate a higher response rate which is associated with a trend for better overall survival, with more rapid response and more subjects bridged to transplant. Despite higher Grade ≥3 AEs in the 10-day regimen, no increase in early mortality was noted with that regimen.

1.5.2 Phase 3 Trial in Previously Untreated AML (Study SGI-110-04)

A Phase 3 study of guadecitabine versus treatment choice is ongoing in adults with previously untreated AML who are unfit to receive or who are not considered candidates for intensive remission induction chemotherapy. The study is a randomized, open-label, multicenter (approximately 100-160 centers) global clinical trial of guadecitabine (60 mg/m^2 Daily×5) versus treatment choice (cytarabine, decitabine, or azacitidine).

1.6 Potential Risks and Benefits to Human Subjects

For a detailed description of risks, refer to the latest version of the Guadecitabine IB. Commonly observed AEs (regardless of relationship to treatment) in Study SGI-110-01 in subjects with AML or MDS include injection site AEs, febrile neutropenia, thrombocytopenia, anemia, diarrhea, fatigue, and nausea. All these AEs and any AEs related to myelosuppression and infection such as pneumonia and sepsis are expected risks of guadecitabine in this Phase 3 trial in r/r AML.

Potential benefits of guadecitabine include symptom improvement, improvement in blood counts, decreased need for transfusions, delayed disease progression, delayed need for subsequent anticancer therapy, and prolongation of survival.

Risk-benefit considerations favor performance of this trial. This study population has limited therapeutic options, and available therapies are of limited utility.

2.0 RATIONALE

2.1 Rationale for the Study

Rationale for this study comes from guadecitabine's molecular structure, PK, pharmacodynamics (PD), and clinical data.

Guadecitabine's dinucleotide structure protects the active decitabine metabolite from inactivation by cytidine deaminase (CDA). 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 FIH Phase 1 SGI-110-01 Dose Escalation, potent DNA demethylation, CR, and other clinical responses were observed in heavily pretreated subjects with AML and MDS, including those previously treated with other existing HMAs (decitabine and azacitidine).

In the Phase 2 SGI-110-01 Dose Expansion in subjects with r/r AML, 24 of 103 subjects responded to treatment with guadecitabine (Table 2), showing that guadecitabine is clinically active in

heavily pretreated subjects with AML. The overall CRc rate was 23.3% (95% CI: 15.5-32.7) and the median overall survival in r/r AML subjects was 197 days (6.6 months [95% CI: 164, 246 days]). In comparison, a recent Phase 3 study comparing a new investigational product (elacytarabine) to treatment choice in r/r AML had similar overall response rates to those found with guadecitabine (CR+CRi of 23% and 21% for elacytarabine and treatment choice groups, respectively) but had lower median survival (3.5 months and 3.3 months for elacytarabine and treatment choice groups, respectively) (Roboz et al 2014).

2.2 Rationale for Guadecitabine Dose and Regimen

In the Phase 2 SGI-110-01 Dose Expansion in subjects with r/r AML, there was no difference in responses or survival between guadecitabine regimens of 60 and 90 mg/m^2 daily for 5 days, so 60 mg/m^2/day was the selected dose. That study in r/r AML subjects also included a 10-day cohort, in which subjects were treated initially with a 10-day regimen (Days 1-5 and Days 8-12) for up to 4 cycles followed by the 5-day regimen in subsequent cycles. A trend for better clinical response was observed in the 10-day group versus the 5-day group, and time to response was faster for subjects in the 10-day group, with more potent demethylation and more subjects bridged to transplant without increase in early mortality.

For the 10-day regimen, the advantages in CRc and time to response must be balanced against the toxicity, as evidenced by higher incidence of AEs than in the 5-day regimen. In particular, the incidence of related Grade ≥3 AEs and related SAEs was higher in the 10-day group compared with the 5-day group. All-cause mortality (30- and 60-day), however, was similar between the regimens, so higher toxicity with the 10-day regimen did not translate to higher mortality. Few subjects in either regimen discontinued treatment due to AEs.

Based on these results for r/r AML, we conclude that the recommended regimen comprises the previously identified BED of 60 mg/m^2/day for 5 days (Days 1-5), with initial intensification (first 1-2 cycles) with 10-day dosing (Days 1-5 and 8-12 or Days 1-10). This regimen, including the initial intensification, appears to facilitate rapid response in heavily pretreated AML subjects with limited additional toxicity and therefore provides the most favorable benefit/risk in this patient population. We recommend limiting the number of cycles of the 10-day regimen to 2 to limit the additional Grade ≥3 AEs.

3.0 STUDY OBJECTIVES

3.1 Primary Objective

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

3.2 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]

4.0 INVESTIGATIONAL PLAN

4.1 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. This global study will be conducted in approximately 20 countries. The study consists of a 14-day screening period, a treatment period, a safety follow-up visit, and a long-term follow-up period. The study is expected to last more than 2 years. The duration of individual subject participation will vary. Subjects may continue to receive treatment for as long as they continue to benefit.

Approximately 404 subjects from approximately 100 study centers will be randomly assigned to either guadecitabine or TC in a 1:1 ratio (approximately 202 subjects per group). (Enrollment was stopped with approximately 300 subjects randomly assigned to treatment [Amendment 4].)

Before randomization, the investigator will assign 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 will be stratified by intensity of preselected TC option (high intensity vs low intensity vs BSC), ECOG performance status (0-1 vs 2), baseline cytogenetics (poor risk vs other; see Appendix 3), and study center region (North America vs ROW).

The TC comparator arm options and doses are described in greater detail in Section 7.2 and treatment duration will be based on approved prescribing information and institutional standard practice. Guadecitabine will be given SC at a dose of 60 mg/m^2 in 28-day cycles. For the first cycle guadecitabine will be given for 10 days on Days 1-5 and Days 8-12 or on Days 1-10. The second cycle will be either the 5-day regimen (Days 1-5) or 10-day regimen (Days 1-5 and 8-12 or Days 1-10) based on assessment of disease response and hematological recovery at the end of Cycle 1. In subsequent cycles guadecitabine treatment will be for 5 days only (Days 1-5). Guadecitabine treatment should be given for at least 6 total 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.

Treatment cycles are intended to be repeated every 28 days. However, treatment delays are permitted to allow normal count hematological recovery in the absence of PB blasts, particularly with more intensive treatment such as guadecitabine 10-day regimen, HiDAC, MEC, and FLAG/Ida. Visits will occur on treatment days, as necessary. In addition, during the first 3 cycles, visits will occur weekly on Days 8, 15, and 22, then on Day 15 in Cycles 4-6. In Cycles >6, visits will only occur on treatment days (if necessary), with study specified assessments on Day 1. Additional visits based on treatment effect and blood counts may be done at the investigator's discretion. Subjects will attend a safety follow-up visit after the last study treatment. For subjects who discontinue study treatment before Cycle 6, long term follow-up visits will occur monthly until 6 months after the start of study treatment and then every 3 months thereafter. For subjects who discontinue study treatment after Cycle 6, long-term follow-up will be every 3 months.

Prior to randomization, administration of hydroxyurea to control high counts is allowed for all subjects. After randomization, subjects in the TC arm may receive hydroxyurea to control proliferative disease as part of study treatment, while subjects in the guadecitabine arm may receive hydroxyurea in the first 30 days of treatment. Subjects randomized to guadecitabine who have proliferative disease between cycles may receive subsequent cycles earlier than the standard 28 days. Subjects with disease progression leading to study therapy discontinuation may receive any other alternative anti-leukemia therapy; however, subjects in the TC arm are not allowed to cross over to guadecitabine.

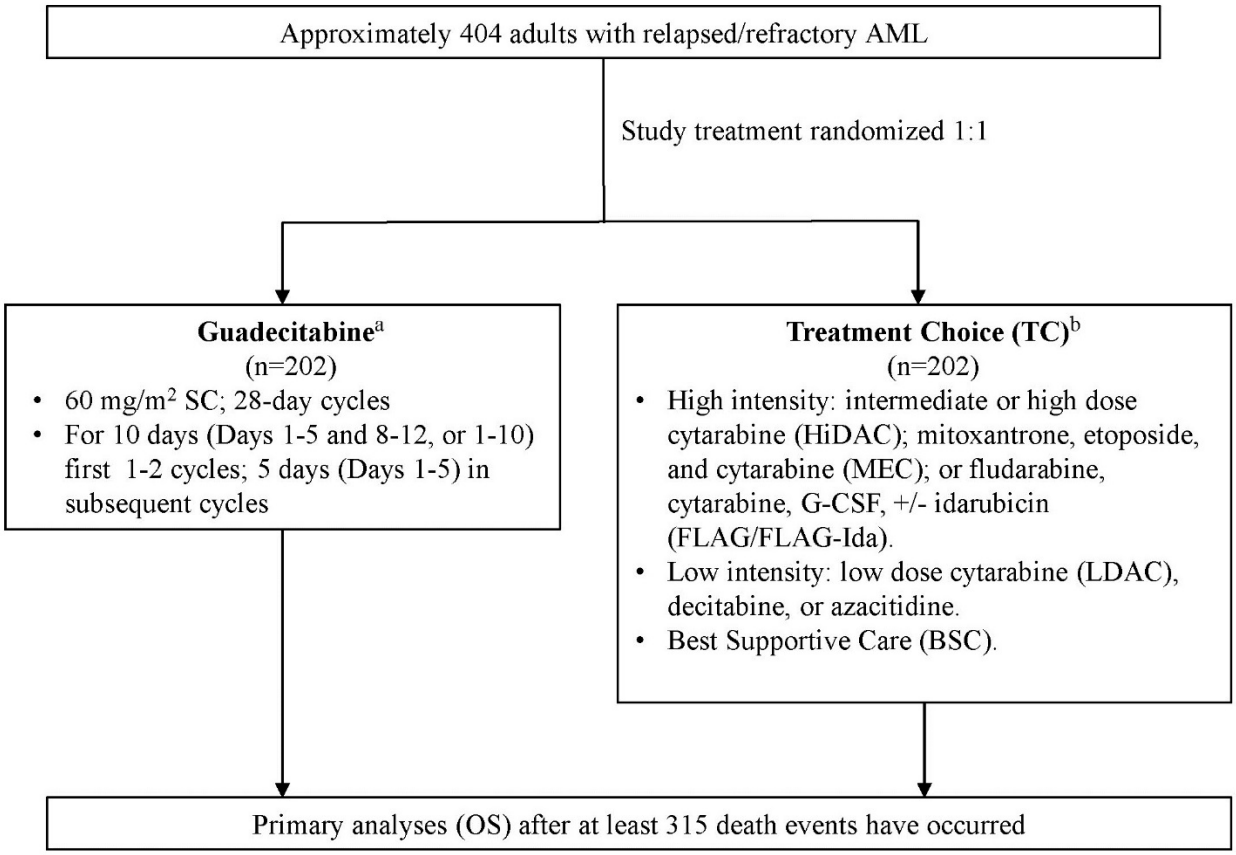
Data will be reviewed by an independent Data Monitoring Committee (DMC) at regular intervals primarily to evaluate safety during study conduct. Based on data from 278 randomly assigned subjects, the DMC recommended to stop further enrollment into the trial based on futility analysis that showed the trial is unlikely to show superiority of guadecitabine over TC for OS. Consequently, the study was closed to further enrollment in September 2018 (Amendment 4).

The primary efficacy endpoint is OS, which will be assessed after at least 315 death events have occurred. One formal interim analysis is planned. The interim analysis will be conducted by an

independent DMC after approximately half of the required death events have occurred. If OS reaches statistical significance in favor of guadecitabine, then the study will be considered positive for efficacy.

Efficacy assessment for the determination of clinical responses will be performed during the first 6 cycles of treatment as well as during long-term follow-up visits. Subjects should be followed for survival information until death, withdrawal of consent, or termination of the clinical trial.

Figure 3: 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.

4.2 Discussion of Study Design

This trial compares the efficacy and safety of guadecitabine to TC in subjects with AML previously treated with induction therapy (even if that induction was not given as first-line therapy) using a

standard intensive chemotherapy regimen or a similar cytarabine+anthracycline based induction, who are refractory to induction or who have relapsed.

Standard intensive induction chemotherapy comprises 7 days of Ara-C and 3 days of an anthracycline (daunorubicin or idarubicin), known as the 7+3 regimen, which produces remission in 70%-80% of patients for whom the treatment is appropriate (Tefferi and Letendre 2012). Less intensive regimens due to patients' age and/or comorbidities are acceptable as long as they include cytarabine and an anthracycline, including the recently approved CPX-351. For patients with relapsed or refractory AML, treatment typically includes diverse regimens of high, medium, and low intensity. Cytarabine is included in many of these regimens, either as a single agent or in combination regimens. HMAs are also used, as discussed in Section 1.2.

TC, the control therapy for this study, includes the treatments listed in Section 4.1. These therapies have not been compared directly, and regional treatment standards vary. Hence, all of these are allowed. TC doses and schedules specified in Section 7.2 are based on prior published reviews and studies (Döhner et al 2015; Roboz et al 2014).

Eligibility criteria for this Phase 3 trial are similar to the eligibility criteria in the preceding Phase 1-2 study. This Phase 3 study additionally requires subjects to have BM or PB blasts ≥5% at randomization.

The randomization ratio of 1:1 maximizes study power for the number of subjects and there is no ethical reason to deviate from the most efficient study design.

OS, the primary endpoint, is accepted as a gold standard endpoint to demonstrate clinical benefit of cancer therapies. Secondary endpoints complement the primary endpoint. Transfusion independence, CR and CRh, days out of hospital, HCT, and quality of life are clinically relevant measures of treatment benefit in this population. Safety will be assessed by comparing incidences of AEs across treatment groups according to the Common Terminology Criteria for Adverse Events (CTCAE) and by 30- and 60-day all-cause mortality.

This study is open-label. The OS primary endpoint is not prone to observer bias. It would be difficult to conduct this trial in a blinded fashion due to differences in treatment schedules and routes of administration among treatment choices. The risk of observer bias in assessing clinical response as a secondary endpoint can be controlled effectively by an independent central reviewer, who will be blinded to treatment assignment (Section 6.2); such review may be conducted if central response assessment is deemed important for benefit/risk assessment at the end of the study.

4.3 Study Endpoints

4.3.1 Primary Endpoint

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

4.3.2 Secondary Endpoints

- EFS defined as the number of days from randomization to the earliest of disease progression, treatment discontinuation, 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 without RBC or platelet transfusion for any period of 8 weeks after treatment.
- CR and CRh rates based on modified IWG 2003 AML Response Criteria.
- 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 VAS).
- Incidence and severity of AEs.
- 30- and 60-day all-cause early mortality.

4.4 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be established for this study. The DMC is a multidisciplinary group consisting of hematologic oncology experts and 1 biostatistician who, collectively, have experience in the treatment of subjects with AML and in the conduct and monitoring of clinical studies. The DMC will independently analyze accumulating data and make recommendations to the sponsor and the Study Steering Committee (SSC), as needed, to continue, modify or discontinue the trial. The DMC will review data at regular intervals, primarily to evaluate safety during study conduct. The DMC will also conduct an independent interim analysis of OS as detailed in Section 11.10 and in a separate DMC Charter.

Details of DMC membership, responsibilities, meeting frequency and format, review materials, and communication plan will also be described in the DMC Charter.

4.5 Study Steering Committee

An SSC composed of the lead investigators in the different study center regions, and sponsor representatives, will be formed to review study conduct at regular intervals, address any issues or recommend changes during the study conduct, and advise the sponsor on implementation of any DMC recommendations. SSC operational details will be described in a separate document.

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Number of Subjects and Centers

Approximately 404 subjects will be enrolled in this study at approximately 100 study centers in approximately 20 countries. (Enrollment was stopped with approximately 300 subjects randomly assigned to treatment [Amendment 4].)

5.2 Inclusion Criteria

To be eligible for the study, subjects must fulfill all of the following inclusion criteria:

1) Adult subjects ≥18 years of age who are able to understand study procedures, comply with them, and provide written informed consent before any study-specific procedure.
2) History of cytologically or histologically confirmed diagnosis of AML (except acute promyelocytic leukemia) according to the 2008 World Health Organization (WHO) classification (BM or PB blast counts ≥20%).
3) Performance status (ECOG) of 0-2.
4) Subjects with AML previously treated with induction therapy using an intensive chemotherapy regimen, defined as a regimen including cytarabine and an anthracycline, and who are refractory to induction (primary refractory) or in relapse after such induction with or without prior HCT.
5) Subjects must have either PB or BM blasts ≥5% at time of randomization.
6) Creatinine clearance or glomerular filtration rate ≥30 mL/min as estimated by the Cockroft-Gault (C-G) or other medically acceptable formulas, such as MDRD (Modification of Diet in Renal Disease) or CKD-EPI (the Chronic Kidney Disease Epidemiology Collaboration).
7) Women of child-bearing potential (according to recommendations of the Clinical Trial Facilitation Group [CTFG]; see below* for details) must not be pregnant or breastfeeding and must have a negative pregnancy test at screening. Women of child-bearing potential and men with female partners of child-bearing potential must agree to practice 2 highly effective contraceptive measures of birth control and must agree not to become pregnant or father a child (a) while receiving treatment with guadecitabine, decitabine, or azacitidine and for at least 3 months after completing treatment and (b) while receiving treatment with high-intensity TC or LDAC and for at least 6 months after completing treatment. Contraceptive measures which may be considered highly effective comprise combined hormonal contraception (oral, vaginal, or transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, sexual abstinence, and surgically successful vasectomy. Abstinence is acceptable only if it is consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of birth control.

* According to recommendations of the CTFG (http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf), a woman is considered of childbearing potential (ie, fertile) following menarche and until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

5.3 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1) Known clinically active CNS or extramedullary AML, except leukemia cutis.
2) Subjects who are in first relapse after initial induction, if they had a response duration of >12 months from the date when first response was documented or if they are good candidates for HCT.
3) BCR-ABL-positive leukemia (chronic myelogenous leukemia in blast crisis).
4) Second malignancy currently requiring active therapy, except breast or prostate cancer stable on or responding to endocrine therapy.
5) Grade 3 or higher Graft Versus Host Disease (GVHD), or GVHD on either a calcineurin inhibitor or prednisone more than 5 mg/day. (Note: Prednisone at any dose for other indications is allowed.)
6) Prior treatment with guadecitabine for any indication, or more than 2 cycles of prior decitabine or azacitidine.
7) Hypersensitivity to decitabine, guadecitabine, or any of their excipients.
8) Treated with any investigational therapy within 2 weeks of the first dose of study treatment.
9) Total serum bilirubin >2.5 × upper limit of normal (ULN) (except for subjects with Gilbert's Syndrome for whom direct bilirubin is <2.5 × ULN), or liver cirrhosis, or chronic liver disease Child-Pugh Class B or C.
10) Known active human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infection. Inactive hepatitis carrier status or low viral hepatitis titer on antivirals is allowed.
11) Known significant mental illness or other condition such as active alcohol or other substance abuse or addiction that, in the opinion of the investigator, predisposes the subject to high risk of noncompliance with the protocol.
12) Refractory congestive heart failure unresponsive to medical treatment; active infection resistant to all antibiotics; or non-AML-associated pulmonary disease requiring >2 liters per minute (LPM) oxygen or any other condition that puts the subject at an imminent risk of death.
13) Subjects with high PB blasts >50% AND poor ECOG PS of 2.

5.4 Treatment Discontinuation and Withdrawal of Subjects

Subjects who discontinue study treatment will be followed up for important study data, as described below, unless they withdraw consent from further follow-up. Medical records or publicly available information may be used to document date of death as needed.

5.4.1 Discontinuation from Study Treatment

Subjects who discontinue study treatment will still continue study follow-up procedures. Investigators are encouraged to assess all subjects according to the study protocol even after discontinuation from study treatment.

- Investigators can discontinue subjects from study treatment in case of unacceptable toxicity, non-compliance, disease progression requiring alternative therapy, or if the investigator determines it is in the subject's best interest.
- Astex Pharmaceuticals may require that a subject is discontinued from treatment for safety reasons or for noncompliance.

In all cases, the reason(s) for discontinuation from study treatment must be recorded in the source document and on the relevant page of the subject's case report form or electronic case report form (CRF/eCRF).

It is important to obtain protocol-specified follow-up information on any subject discontinued from study treatment. Section 10.0 describes follow-up for AEs. Subjects should be followed for survival information until death, withdrawal of consent, or termination of the clinical trial. Safety should be followed for 30 days after the last dose of study treatment, or until the subject starts alternative anti-leukemia treatment for AML (except for hydroxyurea as specified in Section 7.4.1), whichever happens earlier (see Section 10.4). Collection of AEs and concomitant medications may also continue until the decision is made to permanently discontinue study treatment. Subjects in the BSC group will be considered to be on study treatment until they have disease progression.

5.4.2 Withdrawal from the Study

Subjects may withdraw consent for the study at any time, or subjects may be lost to follow-up. The term *withdrawal of consent* should not be used simply because the subject no longer wishes to receive randomized treatment or actively continue to return for follow-up assessments or simply to justify why efforts are not being made to continue to follow some subjects who have discontinued their randomized intervention or wish to participate in another study after discontinuing study treatment. Rather, the term should be used only when the subject no longer wishes to participate in the trial and no longer authorizes the investigators to make efforts to continue to obtain their outcome data. Ideally, if subjects withdraw their consent, it should be done in writing. Investigators will be educated and evaluated about the proper use of the term *withdrawal of consent*, and the DMC will regularly assess whether the term is being used properly.

It is important to obtain follow-up information, according to standard medical practice, on any subject withdrawn prematurely from the study. Every effort must be made to undertake at least standard assessments that are critical for efficacy or safety evaluation, such as disease progression (if the subject did not withdraw because of disease progression), subsequent anti-leukemia treatment, survival information, and safety data.

The investigator must also ensure the subject understands that his or her medical records may continue to be available for the follow-up period as described in the approved informed consent form (ICF).

5.4.3 Replacement of Subjects

Subjects will not be replaced in this study. Astex Pharmaceuticals may stop the study at any time. In this event, Astex will make reasonable efforts to ensure subjects are transitioned off the study in an orderly manner.

6.0 ENROLLMENT, RANDOMIZATION, AND BLINDING PROCEDURES

Subjects will be screened at each study center for assessment of eligibility for the study. Each subject will be assigned a unique number (subject number) which will comprise the center number and the assigned subject number within the center. This number will be used to identify the subject throughout the study.

6.1 Randomization

Eligible subjects will be randomly assigned to study treatment. Treatment assignments for the individual subjects will be determined through a computer generated randomization scheme and accessed through an interactive response system. Instructions for access and use of the interactive response system for randomization will be provided to participating study centers separately.

Randomization will be 1:1 between guadecitabine and TC groups, and will be stratified by intensity of preselected TC option (high intensity vs low intensity vs BSC), ECOG performance status (0-1 vs 2), baseline cytogenetics (poor risk vs other; see Appendix 3), and study center region (North America vs ROW).

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).

6.2 Blinding

The sponsor, investigators, and study subjects are not blinded in this study. However, to minimize the potential bias associated with assessment of treatment outcome, evaluation for response may be performed by a blinded independent central reviewer. The specific process used for handling test samples and reports will be described separately.

7.0 STUDY TREATMENTS

Guadecitabine is the Investigational Medicinal Product (IMP) (Section 7.1), and the active comparator consists of the TC options (Section 7.2).

7.1 Investigational Medicinal Product: Guadecitabine

Guadecitabine (2'-deoxy-5-azacytidylyl-(3'→5')-2'-deoxyguanosine sodium salt) is a dinucleotide incorporating decitabine with deoxyguanosine via a 3'→5' phosphodiester bond.

7.1.1 IMP Information

Guadecitabine (formerly known as SGI-110) [redacted]

SGI-110 for Injection, 100 mg, [redacted]

SGI-110 Diluent for Reconstitution [redacted]

[redacted]

The sponsor recommends following Occupational Safety and Health Administration (OSHA) Guidelines for handling cytotoxic drugs outlined in Yodaiken and Bennett (1986) or similar institutional or country-specific guidelines. Preparation should occur according to institutional practice. For skin contact or spillage, refer to the material safety data sheet (MSDS) for treatment options.

Reconstituted drug product is intended for SC administration at a recommended concentration of 100 mg/mL.

Records of the receipt and dispensing of drug supplies will be kept at the study centers and reconciled at the end of the study to provide a complete accounting of all used and unused IMP.

7.1.2 IMP Regimens and Administration

Guadecitabine will be given SC at a dose of 60 mg/m^2 in 28-day cycles (delayed as necessary to allow blood count recovery, see Section 7.3.1). For the first cycle guadecitabine will be given for

10 days on Days 1-5 and Days 8-12, or in the case of apparent progression during the first 5 days, guadecitabine can be given on Days 1-10 without interruption.

The second cycle will be 60 mg/m^2 for either 10 days (Days 1-5 and 8-12, or in the case of apparent progression, can be Days 1-10) or 5 days (Days 1-5 only) based on assessment of disease response, and hematological recovery at the end of Cycle 1, using the following general guidelines:

- Evidence of active leukemia in PB: no need for BM assessment, give second cycle with 10-day regimen with no delay.
- No evidence of active leukemia in PB: perform BM assessment and decide on course of action as follows:
  - BM blasts ≥5%: give second cycle with the 10-day regimen with no delay.
  - BM blasts <5%: assess recovery of PB normal counts as follows:
    - Absolute Neutrophil Count (ANC) >500/µL ***and*** platelets >50,000/µL: give second cycle with no delay using the 5-day regimen.
    - ANC <500/µL ***or*** platelets <50,000/µL: Delay treatment and repeat PB at least weekly and give second cycle either as a 5-day regimen (if both counts recover to a higher level than the limit above with no PB blasts); or 10-day regimen (appearance of evidence of active leukemia with PB blasts regardless of normal count recovery).

For Cycles ≥3, guadecitabine will be given for 5 days only (60 mg/m^2/day, Days 1-5). These guidelines may be modified if it is believed to be in the best interest of the subject according to the treating physician's best clinical judgment. Treatment should be given for at least 6 total 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. Guadecitabine treatment benefit may not manifest until at least 2 to 3 cycles and full response may need 6 or more cycles (Kropf et al 2015). Maintaining treatment after response is essential to avoid quick relapse (Cabrero et al 2015).

Administer guadecitabine by SC injection, preferably in the abdominal area, upper thigh, or arm. The total amount (in mg) of guadecitabine to be administered is determined by body surface area (BSA). In calculating BSA, use actual heights and weights. Do not adjust to "ideal" body weight. The institutional standard for calculating BSA is acceptable.

Take care to avoid intradermal injection, as this may result in injection site pain (see Section 8.4).

Additional guidelines regarding SC injection will be detailed in the Study Procedures Manual.

Investigators are prohibited from supplying guadecitabine to any subject not enrolled in this study or to any physicians or scientists except those designated as sub-investigators. The investigator must ensure that subjects receive guadecitabine only from personnel who fully understand the procedures for administering the study treatment.

7.2 Active Comparator (Treatment Choice)

The TC options for this study include high intensity, low intensity and BSC. Before randomization, the investigator will assign each subject to one of the following TC options:

High intensity:

- Intermediate or high dose cytarabine (HiDAC), recommended as 1-1.5 g/m^2 every 12 hours or up to 6 g/m^2/day for ≤6 days, maximum 36 g/m^2 per cycle.
- MEC: For example: mitoxantrone 6-12 mg/m^2 IV (recommended 8 mg/m^2), etoposide 80-200 mg/m^2 IV (recommended 100 mg/m^2), and cytarabine 1000 mg/m^2 IV; each daily for 5 days (Days 1-5).
- FLAG/FLAG-Ida: For example: fludarabine 25-30 mg/m^2 IV daily Days 1-5; cytarabine 1-2 g/m^2 IV daily for up to 5 days (recommended to be given for 4 hours after fludarabine); G-CSF SC daily from Day 6 up to white cell count recovery with or without idarubicin 8 mg/m^2 IV daily on Days 3 to 5.

Low intensity:

- LDAC 20 mg SC or IV twice daily on Days 1-10.
- Decitabine 20 mg/m^2 IV daily on Days 1-5.
- Azacitidine 75 mg/m^2 IV or SC daily on Days 1-7.

Best supportive care (BSC) only: given according to standard and institutional practice (refer to Section 7.4.1).

TC administration guidelines and duration will be based on approved prescribing information and institutional standard practice. The above doses and schedules are recommended based on prior published reviews and studies (Döhner et al 2015; Roboz et al 2014); however, small variations of dose, schedule, route, duration of treatment, and dose adjustment guidelines are allowed as long as they follow the locally approved prescribing information or institutional standard practice and are documented in the CRF/eCRF.

Examples of variations in the above regimens include dose reductions in older subjects (> 60 years) or subjects with prior HCT for the high intensity regimens; administering FLAG with no G-CSF; small variations in dose and days of treatment in the cycle; and giving azacitidine as a 5-2-2 schedule instead of 7 consecutive days. Hydroxyurea may be added to any of the TC options to control highly proliferative disease between cycles.

If a subject must discontinue pre-assigned TC study treatment, alternative therapy, if given, should be determined by the physician or institutional standard practice. Subjects randomly assigned to TC study treatment will not be allowed to receive guadecitabine as alternative therapy. HCT is allowed as subsequent treatment for subjects who discontinue treatment in any arm, if it is determined by the investigator that the subject has become eligible for and may benefit from such

treatment. After completion of preassigned TC study treatment, including potential cycles of consolidation with or without reduced intensity (including using fewer drugs) of the same regimen, the addition of any new anti-leukemia therapy for AML treatment that is different from the preassigned TC treatment (with the exception of hydroxyurea to control high WBC count) will be considered "alternative" therapy, and as such will require a subject to discontinue from study treatment.

7.3 Guidelines for Adjusting or Withholding Study Treatment

7.3.1 Guidelines for Guadecitabine

Guadecitabine study therapy is intended to be administered for a minimum of 6 total cycles.

Dosing for the first 2 cycles is described in Section 7.1.2. Timing of cycle initiation and dose level of guadecitabine starting at Cycle 3 will be guided by PB blast and neutrophil/platelet counts after the prior cycle, as indicated in Table 5, which describes dose modification based on Day 29 or later PB counts.

Table 5: Guadecitabine Dosing Adjustment Guideline Based on Peripheral Blood Blasts and Counts (for Cycles ≥3)

Neutrophils Platelets	Peripheral Blood Blasts Present	No Peripheral Blood Blasts		
		On Day 1 of Next Intended Cycle	Recovery After ≤1-Week Dose Delay	Recovery After >1-Week Dose Delay
ANC ≥500/μL **AND** Platelets ≥50,000/μL	Full dose (5-day regimen) on schedule	Full dose (5-day regimen) on schedule	Full dose (5-day regimen) after recovery	Reduce 1 dose level after recovery (5-day regimen)
ANC <500/μL **OR** Platelets <50,000/μL		Consider dose delay or reduction		

For subjects with CRh, CRi or CRp for at least 2 cycles, guadecitabine treatment may be reduced 1 dose level at a time in each subsequent cycle to allow for normal counts recovery to levels of full CR (neutrophils ≥1000/μL and platelets ≥100,000/μL). The highest dose level that achieves normal counts recovery should be kept for subsequent cycles. Recommended reduced guadecitabine dose levels should be from 60 mg/m^2/day to 45 mg/m^2/day, then to 30 mg/m^2/day, and then to 15 mg/m^2/day with the Daily×5 regimen.

Subjects with highly proliferative disease between cycles could receive subsequent cycles earlier than the intended 28-day cycle interval (such subsequent cycles could begin any time after treatment is completed in the preceding cycle).

Beyond 6 cycles, treatment should continue at the dose level reached as long as the subject continues to benefit based on investigator judgment and subject response and tolerability.

7.3.2 Guidelines for Treatment Choice

For scheduling and dose adjustment of TC therapies, refer to the latest locally approved Prescribing Information for each therapy (eg, Cytarabine PI 2015) in the relevant region. Schedule of TC administration may be slightly adjusted in accordance with local standard practice (eg, dosing delay due to hospital closure on weekends or holidays). Dose adjustments should be made according to institutional standards and relevant locally approved Prescribing Information.

7.4 Concomitant Treatment

On the concomitant medication CRF/eCRF, document all medications a subject takes, starting from 14 days before randomization and ending 30 days after the last dose of study treatment, or start of new anti-leukemia treatment for AML (except for hydroxyurea as specified in Section 7.4.1), whichever is first. Collection of concomitant medications may also continue until the decision is made to permanently discontinue study treatment (in the event that this decision occurs more than 30 days after the last dose of study treatment). Prior anti-AML and anti-MDS therapy should be documented regardless of timing with randomization. Include supportive or palliative treatment whether prescription or nonprescription. Include start and stop dates and indication.

7.4.1 Supportive, Prophylactic, or Other Treatments

Supportive care will be allowed in all study arms according to institutional standard practice. Hydroxyurea may be added to any of the TC options to control proliferative disease as part of study treatment. Hydroxyurea is allowed after randomization in the guadecitabine arm in the first 30 days of treatment. If it is given to guadecitabine subjects after the first 30 days, it should be recorded as a deviation but the subject can still continue on guadecitabine study treatment. Intrathecal treatment to control CNS disease is allowed for all subjects as a concomitant treatment. Supportive care includes, but is not limited to treatment with hydroxyurea, blood transfusions (RBCs or platelets), growth factors including erythropoiesis stimulating agents (ESAs), granulocyte stimulating factors (GSFs), iron chelating therapy, and broad spectrum antibiotics and/or antifungals. The investigator is permitted to prescribe supportive treatment(s) at his or her discretion. Give supportive treatment according to the institutional standard practice or other established standard of care guidelines. Investigators are also allowed to give donor lymphocytes infusion (DLI) if it is part of their standard practice in certain subjects with r/r AML. Any supportive or other concomitant treatment should be documented in the provided CRFs/eCRFs.

During treatment cycles of guadecitabine 10-day regimen and all high intensity regimens in the TC arm, prophylactic broad spectrum antibiotics and prophylactic broad spectrum antifungal treatment, with activity against *Aspergillus* species, such as posaconazole and voriconazole are highly recommended.

Once the subject is permanently discontinued from their study treatment due to progression, unacceptable toxicity, bridged to transplant, or any other reason, all subsequent anti-leukemia therapy including HCT or hydroxyurea will be recorded as subsequent anti-AML therapy.

7.4.2 Prohibited Medications

Other anticancer therapies, unless specified in the protocol (eg, endocrine therapy described in exclusion criteria), are not to be used. Cytotoxic chemotherapy and investigational treatments are prohibited for as long as subjects remain on study treatment.

Vaccination with live vaccines is prohibited while subjects remain on study treatment.

7.5 Overdose Instructions

Record the actual dose of study drug administered in the source document and on the Dosing CRF/eCRF. Record any adverse clinical signs and symptoms associated with a potential overdose on the AE CRF/eCRFs. Report signs and symptoms of a potential overdose that meet SAE criteria (defined in Section 10.1.2) to Astex on the SAE form within 24 hours (see Section 10.3). Treat any AE (including SAE) based on standard care for the specific signs and symptoms.

8.0 RISKS/PRECAUTIONS

For guadecitabine, refer to the most recent version of the IB for the most current risks and precautions for guadecitabine, as well as a complete list of AEs considered expected with guadecitabine therapy. For risks and benefits of TC therapies, refer to the latest locally approved Prescribing Information for each therapy.

Since guadecitabine is an investigational drug, unexpected and potentially clinically significant AEs or SAEs may occur with its use. All subjects treated with guadecitabine should be closely monitored. The active metabolite of guadecitabine is decitabine so all events expected with decitabine would also be considered expected for guadecitabine (Dacogen Prescribing Information).

Guadecitabine should not be given to women who are pregnant or to subjects with known sensitivity to decitabine.

8.1 Dose Limiting Toxicities

DLTs related to myelosuppression occurred in 2 subjects with MDS in the Phase 1 Dose Escalation (SGI-110-01) at a dose of 125 mg/m^2 SC Daily×5 and included thrombocytopenia (Grade 4), neutropenia (Grade 4), and sepsis (Grade 5). There were no DLTs in subjects with AML.

8.2 Myelosuppression (Neutropenia, Febrile Neutropenia, Thrombocytopenia, and Anemia)

Myelosuppression is the primary toxicity associated with administration of guadecitabine and its effects after 5 consecutive days of administration are maximal between Days 15 and 22 in a cycle with recovery in 1 to 3 weeks. With the 10-day regimen (dosing on Days 1-5 and 8-12 or on Days 1-10) the nadir is lower and lasts longer than with the 5-day regimen. Pancytopenia is a hallmark of AML and MDS and may aggravate or obscure the effects of guadecitabine. However, if a clinical response occurs and normal hematopoietic cells repopulate the bone marrow, neutropenia and thrombocytopenia may abate.

Complete blood and platelet counts should be performed as needed to monitor counts. Since myelosuppression and infection events are also manifestations of the underlying disease of AML, careful investigator judgment regarding relationship to treatment is important to guide the decision whether to dose delay, dose reduce, or both. The cyclic nature of myelosuppression (reduction of counts between Day 8-15 and trend to recover by Day 22-28 or later) could be more indicative of a drug effect, while persistent low counts regardless of treatment is probably more indicative of a disease effect that needs to be treated without dose delay. Investigators should use their clinical judgment guided by the recommendations for dose adjustment for guadecitabine described above (see Section 7.3.1), and should use the guidelines of dose adjustment for TC options as per their local prescribing information and standard practice.

8.3 Fertility

Use of decitabine, the active metabolite of guadecitabine, alters fertility and is mutagenic. Because of the possibility of infertility, men should seek advice on cryopreservation of sperm, and women of childbearing potential should seek consultation regarding oocyte cryopreservation before study treatment is started. Women of child-bearing potential must not be pregnant or breastfeeding and must have a negative pregnancy test at screening. Women of child-bearing potential and men with female partners of child-bearing potential must agree to practice 2 highly effective contraceptive measures of birth control and must agree not to become pregnant or father a child while receiving treatment with guadecitabine for at least 3 months after completing treatment. Investigators should advise study subjects to seek advice on sperm and oocyte cryopreservation related to TC options as per their local prescribing information and standard practice.

8.4 Injection Site Reactions

Injection site reactions, such as pain, irritation, inflammation, erythema, and burning have been reported in the AML/MDS population and in subjects with solid tumors. Injection site reactions are related to guadecitabine SC administration and are mostly Grade 1 or 2.

Care must be taken to avoid intradermal injection. If injection site pain is reported, it could be avoided or diminished by slow SC injection and the application of ice packs to the injection site both before and after injection. If injection site pain is still clinically significant at subsequent

injections despite slow injection and use of ice packs, pretreatment with topical or systemic analgesics can be considered. In case of injection site pain when injection volume is greater than 1 mL, consider splitting the dose into 2 injections.

8.5 Adverse Events

Most AEs observed in the Phase 1-2 clinical trial are common in the AML/MDS population. Common AEs, regardless of relationship to guadecitabine, observed in the AML/MDS populations (r/r AML, treatment-naïve [TN] AML, TN MDS, r/r MDS, N=308 [Phase 2 Dose Expansion]) treated with guadecitabine (60-90 mg/m^2 Daily×5 or 60 mg/m^2 10-day regimen in AML only) include injection site AEs, febrile neutropenia, thrombocytopenia, diarrhea, fatigue, nausea, anemia, and constipation. The most common SAEs were febrile neutropenia, pneumonia, and sepsis.

MDS and AML subjects commonly have severely compromised bone marrow and blood counts. Severe or prolonged myelosuppression has been reported as related to guadecitabine, particularly at high doses when the drug may exert cytotoxic effects.

Refer to Section 7.3.1 for guidelines to adjust study treatment dose.

9.0 STUDY ASSESSMENTS AND PROCEDURES

9.1 Efficacy Assessments

Efficacy will be assessed by evaluation of survival (OS, EFS, and survival rates at 1 and 2 years), transfusion needs for RBC and platelets (independence and number of transfusions), response (CR, CRh, CRc, CRi, CRp, and partial response [PR]), HCT rate, NDAOH, and health-related QOL.

Survival: Survival will be monitored and documented throughout the study. Survival status will be monitored and recorded as long as possible during the long-term follow-up period.

Transfusions/Hospitalizations: All blood and platelet transfusions will be documented and used to determine transfusion independence and to calculate the number of transfusions. One transfusion is defined as 1 unit of RBC or 1 unit of platelets. Dates and the number of RBC or platelet transfusions will be collected for each subject. Transfusion requirements will be recorded every month in the first 6 months then at every study visit until disease progression. All hospital admissions will be documented and used to determine NDAOH every month in the first 6 months then at every study visit until disease progression. For subjects who discontinue study treatment before Cycle 6, transfusions/hospitalizations will be assessed monthly until 6 months after the start of study treatment, then at every study visit until disease progression.

Response Assessments: Clinical response is based on both PB sampling and BM aspirate or biopsy assessments. If BM aspirate is not available and only BM biopsy slides are provided, slides should include touch prep slides. In cycles where a BM sample is not collected, the most recent previous BM sample will be used for response assessment.

PB will be assessed at baseline and at specified time points in each cycle (see Table 7). BM aspirate or biopsy will be performed at screening and then at the end of Cycles 1, 3, and 6, unless PB shows persistence of ≥5% leukemic blasts that excludes the possibility of a marrow response. After Cycle 6, BM assessment, BM aspirate or biopsy (with touch prep slides) 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 may be done centrally by the independent blinded central reviewer based on BM assessment and PB counts, using the modified 2003 IWG AML response criteria (Cheson et al 2003; Table 6).

Table 6: 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
CRh	Same as CR but with ANC >500/µL and Platelets >50,000/µL	<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	<5% leukemic blasts
Partial response	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 because 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; CRh=complete response with partial hematologic recovery; CRp=complete response with incomplete platelet recovery; CRi=CR with incomplete blood count recovery.
Source: Cheson et al 2003 with modification to define CRh

Best response will be used when a subject experienced different response levels at different visits. Response rate will be calculated for best response categories described below to assess overall efficacy observed.

- CR; CRp and CRi, including the subset of subjects with CRh; partial response.
- Composite CR (CRc=CR+CRp+CRi).

Subjects who did not have a sufficient post-treatment efficacy assessment (eg, no BM or PB assessment) will be classified as nonevaluable for response presentations. These subjects will be included in the denominator of the intent-to-treat (ITT) analysis for calculation of different response rates. Subjects who cannot be classified into a response category (CR, CRp, CRi, partial response) or the nonevaluable category will be classified as nonresponders.

HCT Rate: In subjects who undergo HCT, time to stem cell engraftment and 100-day mortality rate post HCT will be assessed. Time to engraftment will be calculated from the day of transplant to the first day of 3 consecutive days of PB ANC of >500/µL.

Quality of Life: Health-related QOL will be assessed using the EQ-5D™, which is a standardized instrument for use as a measure of health outcome. QOL assessments will consist of the EQ-5D level health questionnaire (EQ-5D-5L) and the EQ VAS which will be administered before treatment on Day 1 of each cycle for 6 cycles and then at every study visit until disease progression; for subjects who discontinue study treatment before Cycle 6, QOL will be assessed monthly until 6 months after the start of study treatment, then at every study visit until disease progression.

[redacted]

9.4 Safety Assessments

Documented safety assessments will include AEs, concomitant medications, physical examination findings, vital signs, electrocardiogram (ECG) measurements, ECOG performance status, and clinical laboratory parameters (hematology and chemistry), according to the schedule of events.

9.5 Study Procedures

9.5.1 Schedule of Events

Table 7 presents the complete schedule of events, with details following in text. Additional information on the study procedures is provided in the Study Procedures Manual.

Clinical and diagnostic laboratory evaluations are detailed before study entry, throughout the study, and at the follow-up evaluation. The purpose of obtaining these detailed measurements is to ensure adequate assessments of efficacy, safety, and tolerability. Repeat clinical evaluations and laboratory studies more frequently if clinically indicated.

Note any deviation from protocol procedures. Investigators are responsible for implementing appropriate measures to prevent the recurrence of violations and deviations and to report to their IRB/IEC according to policy.

Table 7: Schedule of Events

		Cycle 1 - 3									Cycle ≥4							Safety Follow-up[b]	Long-Term Follow-up[c]
Cycle Day		1	2-5	6	7	8 (±2)	9-10	11-12	15 (±3)	22 (±3)	1	2-5	6	7	8 (±2)	9-10	15 (±3)[a]		
Study Treatment[d]																			
Guadecitabine SC[e]		X	X			X[e]	X[e]	X[e]			X	X							
TC: HiDAC ≥1g/m^2/day		X	X	X							X	X	X						
TC: LDAC 20 mg SC twice daily		X	X	X	X	X	X				X	X	X	X	X	X			
TC: MEC		X	X								X	X							
TC: FLAG/FLAG-Ida		X	X								X	X							
TC: Decitabine 20 mg/m^2/day IV		X	X								X	X							
TC: Azacitidine 75 mg/m^2/day IV or SC		X	X	X	X						X	X	X	X					
TC: Best Supportive Care (as needed)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Procedures	**Screening[f] (D -14 to -1)**																		
Informed consent	X																		
Medical history/demographics	X																		
Eligibility assessments	X																		
Physical examination[g]	X	X[g]									X[g]							X	
Vital signs[h]	X	X	X	X[h]	X[h]	X[h]	X[h]	X[h]	X	X	X	X	X[h]	X[h]	X[h]	X[h]		X	
ECOG performance status	X	X									X							X	
12-lead ECG (triplicate)[i]		X																X	
Health-related QOL (EQ-5D)[j]		X									X							X	X[c]
Height	X																		
Weight and BSA calculation (use height from screening)[k]	X	X									X								
Prior anti-leukemia therapies	X																		
AEs/concomitant medications[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization (before dosing)	X[f]																		

Table 7: Schedule of Events (Contd)

		Cycle 1 - 3									Cycle ≥4							Safety Follow-up[b]	Long-Term Follow-up[c]
Cycle Day		1	2-5	6	7	8 (±2)	9-10	11-12	15 (±3)	22 (±3)	1	2-5	6	7	8 (±2)	9-10	15 (±3)[a]		
Laboratory Assessments	**Screening[f] (D -14 to -1)**																		
Hematology[m]	X	X[m]				X			X	X	X[m]						X	X	X[c]
Serum chemistry[n]	X	X[n]									X[n]							X	
Urinalysis	X																		
Serum or urine pregnancy test[o]	X	X									X							X	
[redacted]																			
Disease Assessments																			
BM aspirate or biopsy[r]	X	X[r]									X[r]								X[c]
Cytogenetics	X																		
Hospitalizations/Transfusions[s]	X	X									X							X	X[c]
Subsequent anti-leukemic therapy																		X	X
Disease progression status[t]																		X	X[c]
Survival follow-up																		X	X

[a] The Day 15 visit is not required after Cycle 6.

[b] **Safety follow-up visit:** Must occur 30 (+7) calendar days after the last dose of study treatment or before the subject starts another anti-leukemia therapy for AML (except for hydroxyurea as specified in Section 7.4.1), whichever occurs first. If the subject cannot attend the clinic, the visit may be conducted by telephone to collect, at minimum, AE, hospitalizations/transfusions, subsequent anti-leukemic therapy, QOL responses and survival information. Safety follow-up visit may occur at the same time as treatment discontinuation only if decision to permanently discontinue treatment is made at least 30 days after last dose.

[c] **Long-term follow-up visits:** Start after treatment discontinuation. Monthly (±7 days) visits are required for subjects who discontinue study treatment before Cycle 6, until 6 months after the start of study treatment. After monthly visits for at least 6 months, long-term follow-up visits will be every 3 months (±2 weeks) until death. The first long-term follow-up visit should occur 1 month or 3 months (whichever applies) after the safety follow-up visit or after the last dose of study treatment, whichever applies. Monthly and quarterly visits may be conducted by telephone if needed. Refer to Section 9.5.6 for the specific assessments to be performed at the long-term follow-up visits.

[d] **Study treatment:** For details on all treatment regimens, see Section 7.0. TC duration will be based on approved prescribing information and institutional standard practice. For the TC arm, small variations of dose, schedule, route, duration of treatment, and dose adjustment guidelines are allowed as long as they follow the locally approved prescribing information or institutional standard practice and are documented in the eCRF. BSC subjects are to follow the same 28-day cycle schedule as other subjects, despite not receiving cyclical treatment. Treatment delays are permitted to allow normal hematological count recovery in the absence of PB blasts at the investigator's discretion. Delays due to logistical reasons should be limited to 7 days.

[e] **Guadecitabine treatment:** Cycle 1 will be on Days 1-5 and 8-12 or Days 1-10 (10-day regimen). Cycle 2 will be either the 10-day regimen or the 5-day (Days 1-5) regimen, based on assessment of disease response and hematological recovery by Day ≥28, as specified in Section 7.1.2. Cycle 3 will be the 5-day regimen (Days 1-5).

[f] **Screening (and Randomization):** Screening must occur within 14 days before randomization, except that BM aspirate/biopsy may be collected within 28 days before Cycle 1 Day 1. Cytogenetics should be prior to randomization and may be more than 14 days prior to randomization (see Appendix 3 for cytogenetics-based risk classification). Randomization should occur as close as possible to Cycle 1 Day 1 and may occur on Cycle 1 Day 1. The time between randomization and first treatment should not be more than 1 week.

[g] **Physical examination:** Includes weight and examination of body systems according to institutional standards. A complete physical examination is required. Cycle 1 Day 1 physical examination does not need to be repeated if it was done at screening within 4 days of Cycle 1 Day 1.

[h] **Vital signs:** Assess before dosing on every dosing day in the clinic (based on the subject's assigned treatment regimen), after subject has rested in the sitting position for at least 3 minutes. Subjects in BSC arm: After screening, assess vital signs on Day 1 of every cycle, and at the safety follow-up visit. Vital signs include blood pressure (systolic/diastolic), respiration rate, heart rate, and body temperature. If dosing is done at home (according to local standards), vital signs assessment is not required.

[i] **12-Lead ECG (triplicate):** Conduct predose and 1-2 hours postdose only on Day 1 of Cycle 1, and at safety follow-up visit. Subjects in BSC arm: Conduct ECG (in triplicate) on Cycle 1 Day 1, and at the safety follow-up visit. Acquire and review according to institutional procedure (rhythm, atrial rate, ventricular rate, PR interval, QRS duration, and QT/QTc, morphology and overall interpretation). The QT correction method should be the same for all ECGs for a given subject. Clinically significant abnormal ECG at study treatment discontinuation as compared to the predose ECG should be followed for recovery or stabilization.

[j] **Health-related QOL**: Administer EQ-5D-5L and EQ VAS before treatment on Day 1 of each cycle for 6 cycles, then at every study visit until disease progression. For subjects who discontinue treatment before Cycle 6, administer EQ-5D-5L and EQ VAS monthly until 6 months after the start of study treatment, then at every study visit until disease progression.

[k] **Weight and BSA calculation:** Weigh subjects on Day 1 of each cycle. BSA recalculation is only required if weight changes ±10% or more from the last calculation.

[l] **Concomitant medications:** Document all medications taken within 14 days before randomization to 30 days after the last dose of study treatment, or start of new anti-leukemic treatment for AML (except for hydroxyurea as specified in Section 7.4.1), whichever is first.

[m] **Hematology:** Include complete blood count with WBC differential (a manual count should be conducted if there is suspicion of PB blasts). Day 1 hematology for all cycles does not need to be repeated if done within 4 days of Day 1. Additional hematology assessment may be done for safety or for subject management at the investigator's discretion. Collection, analysis, and reporting information are described in the Study Laboratory Manual.

[n] **Serum chemistry:** Refer to Table 8. Day 1 chemistry for all cycles does not need to be repeated if done within 4 days of Day 1. Additional chemistry assessment may be done for safety or for subject management at the investigator's discretion. Collection, analysis, and reporting information are described in the Study Laboratory Manual.

[o] **Pregnancy test:** Women of child-bearing potential only. The screening test must be done within 7 days of Cycle 1 Day 1 (ie, Day -7 to -1); test not required on Cycle 1 Day 1 if done at screening.

[redacted]

[redacted]

[r] **BM aspirate or biopsy:** BM aspirate and/or biopsy differential count will be performed according to local standard practice. The screening aspirate must be collected within 28 days before starting study treatment. A biopsy should be done if no spicules are observed in the aspirate.
Repeat the BM sample if not interpretable.
Perform BM aspirate/biopsy at screening and then at the end of Cycles 1, 3, and 6 (ie, on or at any time prior to Day 1 of Cycles 2, 4, and 7), unless PB shows persistence of ≥5% leukemic blasts that excludes the possibility of a marrow response. Subjects who discontinue treatment before Cycle 6 Day 1 and before documented disease progression must undergo monthly response assessment until 6 months after the start of study treatment or until disease progression or relapse is confirmed, whichever is first. After Cycle 6, repeat BM aspirate/biopsy every 3 months for the first year on study; BM will be repeated every 6 months thereafter until PB or BM assessment shows disease progression or relapse.

[s] **Hospitalizations/Transfusions:** Document all blood and platelet transfusions (blood product transfused and units) within 56 days before starting study treatment. Document all hospital admission and discharge dates and main reason for hospitalization, as well as all blood and platelet transfusions (blood product transfused and units), from Cycle 1 Day 1 and then monthly to 6 months after the first dose, then at every study visit until disease progression.

[t] **Disease progression status:** For subjects who discontinue study treatment before disease progression is documented, PB and BM aspirate/biopsy assessments as described in footnote "r" should continue until disease progression or relapse is confirmed.

9.5.2 Screening and Baseline Procedures

After the investigator or sub-investigator confirms that a subject is eligible and willing to participate in the study, study center personnel will forward the appropriate documentation to the attention of the sponsor according to the Study Procedures Manual.

Bone marrow aspirate/biopsy samples may be collected within 28 days before Cycle 1 Day 1. Within 14 days before randomization, perform the following study procedures and tests:

- Written informed consent. The ICF must be signed and dated by the subjects before any study-specific samples are collected or study-specific procedures are initiated.
- Complete medical history, including demographics. Record disease history, including the date of initial diagnosis. Document concurrent medical signs and symptoms to establish baseline conditions.
- Record prior anti-leukemic therapies, including start and stop dates, best response and duration of response.
- Record all medications taken within 14 days before randomization.
- Complete physical exam including height and weight, and examination of body systems according to institutional standards.
- Vital signs include resting systolic/diastolic blood pressure, resting respiration rate, resting heart rate, and body temperature.
- Serum or urine pregnancy test: for women of child-bearing potential only. Results must be negative for the subject to be eligible for enrollment into the study.
- ECOG performance status (Appendix 1).
- Height measurement (for BSA calculation).
- All study-procedure-related AEs from the time of informed consent.
- Blood and urine sample collection for clinical laboratory tests (Table 8).
- [redacted].
- Adequate BM aspirate slide or biopsy to include touch prep slide, collected within 28 days before starting study treatment.
- Cytogenetic assessments performed at any time before randomization.
- Document all blood and platelet transfusions (blood product transfused and units) performed within 56 days before randomization.
- Investigator's confirmation of eligibility. Perform all necessary procedures and evaluations to document that the subject meets each eligibility criterion.

- Study treatment randomization, after eligibility is confirmed. Randomize as close as possible to the first dose of study treatment (on Cycle 1 Day 1). Treatment should start as soon as possible after randomization, and in all cases within 1 week.

Table 8: Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis	Serology
Complete blood count (CBC) - Hemoglobin - Hematocrit - RBC counts - WBC counts - Platelets WBC differential (a manual count should be conducted if there is suspicion of PB blasts) - Blasts - Promyelocytes - Myelocytes - Metamyelocytes - Monoblasts - Promonocytes - Neutrophils - Band neutrophils - Segmented neutrophils - Eosinophils - Basophils - Lymphocytes -Monocytes	- Albumin - Alkaline phosphatase - ALT - AST - BUN - Calcium - Chloride - Creatinine - Glucose - Magnesium - Potassium - Sodium - Total bilirubin - Direct bilirubin (only if medically indicated) - Total protein	- Dipstick (analysis based on institutional standards) - Pregnancy test (if applicable)	- Pregnancy test (if applicable)

9.5.3 Treatment Procedures for Cycles 1-3

The following text represents assessments and procedures for Cycles 1, 2, and 3, unless otherwise specified (eg, PK and ECG assessments are done only in Cycle 1). Refer to Table 7.

After randomization, visits will occur on every treatment day, as necessary. In addition, visits will occur on Days 8, 15 and 22 of the first 3 cycles of therapy. Additional visits, based on treatment effect and blood counts may be done at the investigator's discretion.

9.5.3.1 Day 1 (Before Dosing), Cycles 1-3

- Complete physical examination (does not need to be repeated if was done ≤4 days before Cycle 1 Day 1).
- Vital signs.
- ECOG performance status (Appendix 1).
- 12-lead ECG (triplicate) (rhythm, atrial rate, ventricular rate, PR interval, QRS duration, and QT/QTc, morphology and overall interpretation), Cycle 1 only.

- Health-related QOL (Appendix 2).
- Weight and BSA calculation (use height from screening; BSA recalculation is only required if weight changes ±10% or more from last calculation).
- Cycle 1: All study-procedure-related AEs and concomitant medications.
- Cycles 2-3: All AEs and concomitant medications.
- Sample collection for laboratory assessments, including:
  - Hematology (see Table 8) (does not need to be repeated if done ≤4 days before Day 1).
  - Serum chemistry (see Table 8) (does not need to be repeated if done ≤4 days before Day 1).
  - Serum or urine pregnancy test for women of child-bearing potential only (for Cycle 1 Day 1 does not need to be repeated if done at screening within 7 days of C1D1).
- BM aspirate/biopsy required at the end of Cycle 1 (ie, Day 1 of Cycle 2) unless PB shows persistence of ≥5% leukemic blasts that excludes the possibility of a marrow response.
- [redacted]
- Hospital admission and discharge dates (and the main reason for hospitalization), as well as all blood and platelet transfusions (blood product transfused and units) since Day 1 of previous cycle.

9.5.3.2 Day 1 (After Dosing), Cycles 1-3

- 12-lead ECG (triplicate), in Cycle 1 only, 1 to 2 hours postdose. ["Postdose" ECG not required for subjects randomized to the BSC arm.]
- [redacted]
- Cycle 1: All treatment-emergent AEs and concomitant medications.

9.5.3.3 Other Dosing Days, Cycles 1-3

- Vital signs (before dosing).
- All AEs and concomitant medications.
- [redacted]

9.5.3.4 Days 8, 15 and 22, Cycles 1-3

The following procedures will be performed on Days 8 (±2), 15 (±3), and 22 (±3) of Cycles 1-3.

- Vital signs (to be performed before dosing on Day 8, if applicable).

- All AEs and concomitant medications.
- Hematology (see Table 8).

9.5.4 Treatment Procedures for Cycles ≥4

Table 7 shows assessments and procedures for Cycles ≥4. For Cycles 4-6, visits will occur on every treatment day (as necessary) and on Days 1 and 15. In Cycles >6, only treatment day visits are required (if necessary), with study-specified assessments required only on Day 1. Additional visits, based on treatment effect and blood counts may be done at the investigator's discretion. Subjects will attend a safety follow-up visit after the last study treatment and long-term follow-up thereafter.

9.5.4.1 Day 1 (Before Dosing), Cycles ≥4

- Complete physical examination.
- Vital signs.
- ECOG performance status (Appendix 1).
- Health-related QOL (Appendix 2).
- Weight and BSA calculation (use height from screening; BSA recalculation is only required if weight changes ±10% or more from last calculation).
- All AEs and concomitant medications.
- Sample collection for laboratory assessments, including:
  - Hematology (see Table 8).
  - Serum chemistry (see Table 8).
  - Serum or urine pregnancy test for women of child-bearing potential only.
- BM aspirate/biopsy required at the end of Cycles 3 and 6 (ie, on or before Day 1 of Cycles 4 and 7) unless PB shows persistence of ≥5% leukemic blasts that excludes the possibility of a marrow response. Subjects who discontinue treatment before Cycle 6 Day 1 and before documented progression must undergo response assessment until disease progression or relapse is confirmed. After Cycle 6, repeat BM aspirate/biopsy every 3 months for the first year on study, then every 6 months thereafter until PB or BM assessment shows disease progression or relapse.
- Hospital admission and discharge dates (and the main reason for hospitalization), as well as all blood and platelet transfusions (blood product transfused and units) since Day 1 of the previous cycle.

9.5.4.2 Day 1 (After Dosing), Cycles ≥4

- [redacted]

9.5.4.3 Other Dosing Days in Clinic, Cycles ≥4

- Vital signs (before dosing).
- All AEs and concomitant medications.

9.5.4.4 Day 15, Cycles 4 to 6

Day 15 for Cycles 4 to 6 has a visit window of ±3 days.

- All AEs and concomitant medications.
- Hematology (see Table 8).

9.5.5 Safety Follow-up Visit

Subjects will attend a safety follow-up visit after study treatment has been permanently discontinued. The safety follow-up visit must occur 30 (+7) calendar days after the last dose of study treatment or before the subject starts another anti-leukemia therapy for AML (except for hydroxyurea as specified in Section 7.4.1), whichever occurs first.

Each subject should be followed, to document the occurrence of any new AEs, for at least 30 (+7) days after his or her last dose of study treatment, or until any AE or SAE assessed as related to study treatment or procedures has resolved to a clinically acceptable or stable resolution (see Section 10.3).

Subjects who withdraw consent should still be encouraged to complete this visit. The following evaluations are to be performed:

- Complete physical examination.
- Vital signs.
- ECOG performance status (Appendix 1).
- 12-lead ECG (triplicate).
- Health-related QOL (Appendix 2).
- All AEs and concomitant medications.
- Sample collection for clinical laboratory tests, including:
  - Hematology (see Table 8)
  - Serum chemistry (see Table 8)

  - Serum or urine pregnancy test for women of child-bearing potential only.
- Hospital admission and discharge dates (and the main reason for hospitalization), as well as all blood and platelet transfusions (blood product transfused and units) since they were last recorded.
- Subsequent anti-leukemic therapy (regimen and start date); for HCT, include time to stem cell engraftment.
- Disease progression status: Subjects who discontinue study treatment before documented disease progression must undergo response assessments (PB or BM aspirate/biopsy) until disease progression or relapse is confirmed.

If the subject is not able to attend the clinic for the safety follow-up visit, the visit may be conducted by telephone to collect at minimum AE information, hospitalization information, transfusion information, subsequent anti-leukemic therapy, QOL responses, and survival status. If a decision is made to permanently discontinue study treatment ≥30 (+7) days after the last dose, then the 30-day safety follow-up visit should be performed as soon as possible on the day the discontinuation decision is made or as soon as possible thereafter.

9.5.6 Long-Term Follow-up

Long-term follow-up starts after subjects discontinue study treatment. Long-term follow-up visits will occur monthly (±7 days) for subjects who discontinue study treatment before Cycle 6, until 6 months after the start of study treatment. After monthly visits for at least 6 months after the start of study treatment, long-term follow-up visits will be every 3 months (±2 weeks) until death. The first long-term follow-up visit should occur 1 month or 3 months (whichever applies) after the safety follow-up visit or after the last dose of study treatment, whichever applies. Long-term follow-up visits may be conducted by telephone if needed.

At the **monthly** long-term follow-up visits, the following assessments are required unless they are refused by the subject. However, at a minimum, information on survival status must be collected.

- Health-related QOL (Appendix 2).
- Hematology and/or BM aspirate/biopsy: Subjects who discontinue study treatment before documented disease progression must undergo response assessments (PB or BM aspirate/biopsy) until disease progression or relapse is confirmed.
- Hospital admission and discharge dates (and the main reason for hospitalization), as well as all blood and platelet transfusions (blood product transfused and units) since the last visit.
- Subsequent anti-leukemic therapy (regimen and start date); for HCT, include time to stem cell engraftment.
- Survival follow-up (must be collected).

At the **quarterly** long-term follow-up visits, the following assessments are required unless they are refused by the subject. However, at a minimum, information on survival status must be collected.

- Health-related QOL (Appendix 2) until disease progression.
- Hematology and/or BM aspirate/biopsy: Subjects who discontinue study treatment before documented disease progression must undergo response assessments (PB or BM aspirate/biopsy) until disease progression or relapse is confirmed.
- Hospital admission and discharge dates (and the main reason for hospitalization), as well as all blood and platelet transfusions (blood product transfused and units) since the last visit until disease progression.
- Subsequent anti-leukemic therapy (regimen and start date); for HCT, include time to stem cell engraftment.
- Survival follow-up (must be collected).

9.6 Unscheduled Visits

Additional visits (not specified in Table 7) may be conducted for PB assessment, BM aspirate/ biopsy, chemistry assessment, or AE evaluation, at the investigator's discretion.

9.7 Missed Evaluations

Evaluations should occur within the visit window specified by the protocol. If an evaluation is missed, reschedule and perform it as close as possible to the original date. If rescheduling becomes, in the investigator's opinion, medically unnecessary because the evaluation would occur too close to the next scheduled evaluation, it may be omitted. For guadecitabine dosing, if a dose is missed on one or more days, it should be administered as soon as possible to complete the full 5-day course (see Section 7.3.1). For TC dosing, if a dose is missed, it should be made up in a manner consistent with institutional standards (see Section 7.3.2).

10.0 EVALUATION, RECORDING, AND REPORTING OF ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Event (AE)

Adverse Event (AE): Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal finding in laboratory tests or other diagnostic procedures), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug and from any route of administration, formulation, or dose, including an overdose.

Disease progression is not considered to be an AE or serious adverse event (SAE). If there are specific AEs that are always part of disease progression, these do not need to be reported as AEs

or SAEs. Pre-existing medical conditions (other than natural progression of the disease being studied) judged by the investigator or subject to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period will be reported as AEs or SAEs as appropriate.

An AE or SAE can also be a complication that occurs as a result of protocol mandated procedures (eg, invasive procedures such as biopsies).

10.1.2 Serious Adverse Events (SAEs)

An AE is considered serious, if in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death.
- A life-threatening AE.

  An AE is considered "life-threatening" if in the view of either the investigator, or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of an existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.

Important medical events that may not result in death, be life-threatening or require hospitalization may be considered serious when, based on the appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE. Examples of such medical events are intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or development of drug dependency or drug abuse. For clarification, Grade 3 or 4 cytopenias that are not associated with a life-threatening or otherwise medically significant clinical AE as defined above, and do not result in hospitalization, are not considered SAEs.

10.2 Adverse Event Reporting and Descriptions

Record new AEs from the start of study treatment until 30 days after the last dose of study treatment or until the subject starts new anti-AML treatment, including new investigational treatment, whichever occurs first. Collection of AEs may also continue until the decision is made to permanently discontinue study treatment. Related SAEs should be collected until the end of the study or the subject’s death. Record screening procedure-related AEs that occur before the start of study treatment.

Record all AEs either observed by the investigator or one of his or her medical collaborators, or reported by the subject spontaneously, or in response to the direct question below, in the AEs section of the subject's CRF/eCRF, in the source document, and if applicable, record on the SAE form. Whenever possible, the investigator should group signs and symptoms (including laboratory tests or other results of diagnostic procedures) into a single diagnosis under a single term. For example, cough, rhinitis, and sneezing might be reported as "upper respiratory infection" or a pulmonary infiltrate, positive sputum culture and fever might be reported as "pneumonia."

To optimize consistency of AE reporting across centers, ask the subject a standard, general, non-leading question to elicit any AEs (such as "Have you had any new symptoms, injuries, illnesses since your last visit?").

Death is an outcome of an SAE and usually not itself an SAE, unless it is death with no identifiable cause or event. In all other cases, record the cause of death as the SAE. Investigators will assess the status of previously reported, and occurrence of new AEs and SAEs at all subject evaluation time points during the study.

10.2.1 Severity

Use the definitions found in the CTCAE version 4.03 for grading the severity (intensity) of AEs. The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE and provides guidance not listed. Should a subject experience any AE not listed in the CTCAE v4.03, use the following grading system to assess severity:

- Grade 1 – Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 – Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL), such as preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Grade 3 – Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL, such as bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
- Grade 4 – Life-threatening consequences; urgent intervention indicated.
- Grade 5 – Death related to AE.

10.2.2 Relationship to Study Treatment (Suspected Adverse Reactions)

Assess all AEs/SAEs for relationship to study treatment or if applicable, to study procedure.

If an AE/SAE occurs before the first dose of study treatment, report it only if it is considered related to a study-specific procedure (eg, bleeding or local infection after skin punch biopsy). Those events will be recorded in the study database but will not be part of the treatment- emergent AE analysis.

To ensure consistency of AE and SAE causality assessments, investigators should apply the general guideline shown below. Multi-drug regimens should have a causality assessment of each component to aid in analysis.

Related (Suspected Adverse Reaction)	A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE such as a plausible temporal relationship between the onset of the AE and administration of the drug; and/or the AE follows a known pattern of response to the drug; and/or the AE abates or resolves upon discontinuation of the drug or dose reduction and, if applicable, reappears upon rechallenge. Further examples of type of evidence that would suggest a causal relationship between the drug and the AE: • A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, hepatic injury, Stevens-Johnson Syndrome), • One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (eg, acute myocardial infarction in a young woman), • An aggregate analysis of specific events observed in a clinical study (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group that in a concurrent or historical control group.
Not Related (Not Suspected)	Adverse events that do not meet the definition above.

10.2.3 Pregnancy and Abortion

Report any pregnancy that occurs in a subject or male subject's female partner during the time between the first study-specific procedure and 60 days after the last dose of study treatment. Record any occurrence of pregnancy on the Pregnancy Report Form Part I and fax to Astex Pharmaceuticals Drug Safety within 24 hours of learning of the event. After the birth of the baby, collect additional information on the baby until the baby is 1 year old by completing the Pregnancy Report Form Part II.

A subject must immediately inform the investigator if the subject or subject's partner becomes pregnant during the time between the first study-specific procedure and 60 days after the last dose of study treatment. Any female subjects receiving guadecitabine who become pregnant must

immediately discontinue study treatment. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Report any abortion and the reason for it, whether therapeutic, elective or spontaneous, to Astex Pharmaceuticals Drug Safety within 24 hours, through the SAE reporting process (Section 10.3).

10.3 Reporting and Evaluation of Serious Adverse Events

10.3.1 Reporting Requirements for Serious Adverse Events (SAEs)

All SAEs regardless of causality will be reported by the investigator to Astex Pharmaceuticals through the 30-day period after the last dose of study treatment. Deaths and SAEs occurring after the 30-day safety follow-up period AND considered related to study treatment or study procedures must also be reported.

Report all SAEs (initial and follow-up information) on an SAE form and send the form to Astex Pharmaceuticals Drug Safety, or designee, within 24 hours of the discovery of the event or information (see below). Astex Pharmaceuticals may request follow-up and other additional information from the investigator (eg, hospital admission or discharge notes, laboratory results).

Astex Pharmaceuticals Drug Safety Contact Information	
PRIMARY CONTACT: Email	[redacted]
Global Phone	[redacted]
North America Toll-Free Fax	[redacted]

Report all deaths with the primary cause of death as the SAE term, as death is the outcome of the event, not the event itself. If an autopsy was performed, report the primary cause of death on the autopsy report as the SAE term. Forward autopsy and postmortem reports to Astex Pharmaceuticals Drug Safety, or designee, as outlined above.

If study treatment is discontinued, temporarily suspended or dose reduced because of an SAE, include this information in the SAE report.

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SAEs that qualify for mandatory expedited reporting to regulatory authorities where the SAE is suspected to be caused by the study treatment and is considered unexpected (ie, not defined as expected in the current IB clinical study protocol, or approved labeling for marketed drugs). In this case, Astex Pharmaceuticals Drug Safety or designee will report to the relevant regulatory authorities and forward a formal notification describing the SUSAR to investigators, according to regulatory requirements. Each investigator must then notify his or her IRB/IEC of the SUSAR as required by local regulatory authorities and in accordance with IRB/IEC policy.

10.4 Follow-up for Adverse Events

Follow all AEs and SAEs that are encountered during the protocol-specified AE reporting period until (1) they are resolved, or (2) the investigator assesses the subject as stable and the event follows a clinically expected outcome, or (3) the subject is lost to follow-up, discontinues long-term follow up (except for survival), or withdraws consent.

11.0 STATISTICS

Statistical analyses will be performed by Astex Pharmaceuticals or its designee.

Data summaries and listings will be generated using SAS version 9.3 or a more recent version (SAS Institute Inc., Cary, NC, USA).

The statistical analysis plan and/or the clinical study report will provide additional details of the analysis, which may include details of missing and, if applicable, unused data, as well as additional sensitivity analyses of the primary and secondary variables. The clinical study report will describe deviations from the statistical analysis plan, if any.

11.1 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 enrolment will be non-uniform over an 18 month period (with additional follow up of 8 months) during which 3 to 29 subjects per month (3, 6, 9, 12, 15, 18, 21, 24, 27, and 29) are 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 need to be randomized. If, after a follow up of 12 months from the last subject randomized, the 315 death events have not occurred, the primary analysis will be conducted at 12 months from last subject randomized (if 277 or more death events have occurred), or after at least 277 death events have been observed (corresponding to 86% power). Based on DMC recommendation to stop further enrollment, the time of primary analyses is 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.

11.2 Analysis Sets

11.2.1 All-Subjects Analysis Set

The All-Subjects Analysis Set will contain information from all screened subjects, including those who did not meet the study entry criteria or did not receive a study treatment.

11.2.2 Efficacy Analysis Set

Efficacy analyses will be based on the 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, the primary analysis sets 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 sets may also include additional data (eg, data collected over the entire study).

11.2.3 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.

[redacted]

11.3 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 Section 4.4). An interim analysis of OS was planned to be conducted by the DMC when approximately half of the required 315 death events have occurred. However, at the DMC meeting on 12 September 2018, after approximately one-third of the required 315 death events had occurred, the DMC recommended to discontinue enrollment based on futility, so no further interim analysis will be conducted.

To achieve a mature analysis of OS and also keep the study duration within a reasonable period, the primary analysis was to be conducted either after 315 death events (corresponding to a 90% power) have occurred within 12 months from the date of the last subject randomization, or at

12 months from last subject randomized (if 277 or more death events occurred by then), or after at least 277 death events (corresponding to an 86% power) have been observed. Refer to Section 11.1; the time of primary analyses is 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.

11.4 Disposition

Subject disposition including numbers screened, randomized, treated, treatment discontinuation by reason, and withdrawal from study by reason will be summarized for each treatment group (guadecitabine and TC) and both treatment groups combined. Sample sizes for Efficacy and Safety Analysis Sets will be clearly identified. The All-Subjects Analysis Set will be used for the disposition analysis.

11.5 Analysis of Demographic and Baseline Data

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. The Efficacy and Safety Analysis Sets will be used for the summaries. The summaries will be done for each treatment group (guadecitabine and TC) and both treatment groups combined.

11.6 Efficacy Analyses

Efficacy analyses will be presented by treatment group (guadecitabine vs TC) 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 315 deaths 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 for analysis of each endpoint in the hierarchical testing, accounting for the alpha spent in the interim analysis. 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 will be specified in the statistical analysis plan.

If the primary endpoint reaches statistical significance in favor of guadecitabine, the study will be considered positive in efficacy.

11.6.1 Primary Efficacy Analysis

OS is the primary endpoint and is defined as the number of days from the day the subject was randomized to the date of death (regardless of cause). Subjects without a documented death date will be censored on the last date known to be alive.

OS will be displayed using a Kaplan-Meier estimate and will be compared between the 2 treatment groups using a log-rank test stratified by the randomization stratification factors with an overall 2-sided alpha level of 0.05. In order to control the overall type I error rate at 0.05 (2-sided), the nominal alpha to be used in the final analysis will be calculated accounting for the alpha already spent at the interim analysis.

In addition, the hazard ratio and the 95% CI will be estimated using a Cox proportional-hazard model with treatment as the independent variable and stratified by the same randomization stratification factors as used for the log-rank test.

11.6.2 Secondary Efficacy Analyses

Response will be assessed in each cycle using both PB and BM. In cycles where BM is not available, the most recent prior BM will be used.

Secondary efficacy endpoints are the following and will be defined in more detail in the statistical analysis plan:

- EFS defined as the number of days from randomization to the earliest date of disease progression, treatment discontinuation, 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.
- CR and CRh rates based on modified IWG 2003 AML Response Criteria, as described in Section 9.1.
- CRc (CR+CRi+CRp) rate, as described in Section 9.1.
- 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 VAS).

If statistical significance is achieved for OS, hierarchically EFS, 1-year survival rate, NDAOH, transfusion independence rate, combined CR+CRh rate, CRc rate, and HCT rate will be compared between the two treatment groups as addressed in Section 11.6.2. The alpha level for the secondary endpoints involved in statistical testing depends on results of previous hierarchical testing and on whether early termination of the study occurs after the interim analysis.

11.6.2.1 Event-free Survival (EFS)

EFS is defined as the number of days from randomization to the earliest of disease progression, treatment discontinuation, start of alternative anti-leukemia therapy (except for HCT), or death.

Disease progression is defined as earliest occurrence of one of the following:

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

EFS will be displayed using a Kaplan-Meier estimate and will be compared between the two treatment groups using a log-rank test stratified by the randomization stratification factors. EFS time will be censored on the last date the subject is known to be alive without an EFS event.

11.6.2.2 Survival rate at 1 Year

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 the Kaplan-Meier procedure. Hypothesis testing will be based on the stratified Kaplan-Meier estimates and standard errors estimated by Greenwood formula. 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 also be determined.

11.6.2.3 Number of Days Alive and Out of the Hospital

The date of each hospital admission and discharge will be collected for each subject. The number of days when subjects are still alive and out of hospital during the first 6 months of the study will be summarized by treatment group and compared between the 2 treatment groups using an analysis of variance model, which includes treatment group and all randomization stratification factors in the model.

11.6.2.4 Transfusion Independence Rate

Transfusion independence rate is calculated as number of subjects without RBC or platelet transfusion for any period of 8 weeks after treatment 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. In addition, the Mantel-Haenszel weighted difference in transfusion independence rate between the 2 treatment groups and the associated CI will be provided.

11.6.2.5 Complete Response and Complete Response with Partial Hematologic Recovery Rates

The CR and CRh rates will be calculated individually and combined as the number of subjects with 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. In addition, the Mantel-Haenszel weighted difference in CR, CRh, and combined CR+CRh rates between the 2 treatment groups and the associated CI will be provided.

11.6.2.6 Composite CR Rate

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 stratified by the stratification variables. In addition, the Mantel-Haenszel weighted difference in CRc rate between the 2 treatment groups and the associated CI will be provided.

11.6.2.7 Hematopoietic Cell Transplant Rate

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. In addition, the Mantel-Haenszel weighted difference in HCT rate between the 2 treatment groups and the associated CI will be provided.

Time-to-stem-cell engraftment is calculated, for subjects who received an HCT after randomization, from the day of transplant to the first day of 3 consecutive days of PB ANC of >500/μL. Time-to-stem-cell engraftment will be summarized by treatment group.

One hundred-day post-HCT mortality rate (regardless of cause) will be calculated for subjects who received an HCT after randomization, and summarized by treatment group.

11.6.2.8 Duration of Combined CR and CRh

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

11.6.2.9 EQ-5D-5L

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). The EQ-5D-5L index value and VAS and their respective changes from baseline will be summarized by visit. Only the data collected in the first 6 months of the study will be included in this analysis. In addition, the changes from baseline of EQ-5D-5L index value, and separately EQ VAS, will be analyzed using a mixed model approach for repeated measures.

11.6.2.10 Sequence of Statistical Tests for Efficacy Endpoints

The primary endpoint OS will be tested first. If the test for OS is positive, hypothesis testing will proceed for the secondary endpoints in the following order:

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

A positive test result of the earlier endpoint serves as a gatekeeper (Westfall and Krishen 2001) for analysis of the next endpoint. Other secondary efficacy endpoints (duration of CR and Health Related QOL) will be used as supportive evidence of the beneficial treatment effect. Differences of treatment effect for these endpoints and associated 95% CIs, if applicable, will be constructed.

11.6.3 Subgroup and Exploratory Analyses

Subgroup analyses will be performed to explore how OS is influenced by baseline variables and the individual TC therapy administered, and to evaluate the treatment effect at different levels of each of these variables. The Kaplan-Meier analysis and Cox model will be performed by subgroup levels of the baseline variables and each TC therapy listed below:

- Age (<75, ≥75).
- Baseline cytogenetic risk (poor-risk, others; see Appendix 3).
- ECOG performance status (0-1, 2).
- Number of prior regimens (≤2, >2).
- Prior HCT (yes, no).
- Baseline BM blasts (≤40%, >40%).

- Baseline total WBC counts (≤20,000/µL, >20,000/µL).
- Study center region (North America, Europe, Asia-Pacific, Other).
- Race (White, Black, Asian, Other).
- Presence of baseline specific gene mutations or gene expressions for each gene (yes, no).
- Individual preselected TC (high intensity, low intensity, BSC).
- Additional subgroups may also be further described in the Statistical Analysis Plan.

11.7 Safety Analyses

The Safety Analysis Set will be used for all safety analyses. Safety will be 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. Safety will also be assessed by exposure to guadecitabine or TC, reasons for discontinuation, deaths, and causes of deaths.

AEs will be mapped to the appropriate System Organ Class (SOC) and PT according to the Medical Dictionary for Regulatory Activities (MedDRA). Severity of AEs will be graded using CTCAE version 4.03. All AEs collected during the study will be presented in data listings. Treatment-emergent AEs will also be analyzed with summary tables. Treatment emergent AEs are defined as events that first occurred or worsened after the first dose of study drug given on Cycle 1 Day 1 (C1D1) until 30 days after the last dose of study treatment or the start of an alternative anti-leukemia treatment for AML (except for hydroxyurea as specified in Section 7.4.1), whichever occurs first, as to be defined in more detail in the statistical analysis plan. The summary will be provided for all AEs, AEs considered related to study treatment, SAEs, and related SAEs as follows:

- By maximum severity.
- Incidence by SOC (by severity grade and overall).
- Incidence by PT (by severity grade and overall) within each SOC.

Thirty- (30) and 60-day all-cause mortality rates will be calculated as number of deaths, regardless of cause, within 30 or 60 days from the first study dose (C1D1) divided by the total number of subjects included in the safety analysis set. The 30- and 60-day mortality rates and their 95% CIs will be provided for each treatment group.

Laboratory values will be graded, if applicable, by CTCAE in conjunction with Harrison (18th edition) lab book normals (Longo et al 2011). Shift tables will be provided for each graded laboratory test.

Concomitant medications are the medications taken with a start date on or after the start of the administration of the study drug (C1D1), or those with a start date before the start of study drug

administration (C1D1) and a stop date on or after the start of study drug administration (C1D1), as to be defined in more detail in the statistical analysis plan. Concomitant medication will be coded by the WHO Drug Dictionary and summarized by Therapeutic subgroup (ATC level 2) and PT, sorted alphabetically, using counts and percentages.

Vital sign measurements will be summarized by visit using proportion of subjects with each vital sign being too high or too low according to conventionally accepted vital sign normal ranges. Physical examination, ECOG and ECG findings will be listed in data listings or analyzed with summary tables.

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11.10 Interim Analysis

One interim analysis of OS is planned with a maximum spendable alpha of 0.01. This interim analysis was be conducted by the independent DMC after approximately half of the required 315 death events have occurred. The nominal alpha values for the interim and final 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 0.04998, respectively. The actual alpha value to be used in the final analysis will depend on the actual alpha spent for the interim analysis. 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).

Refer to Section 11.3 for the schedule of analyses.

11.11 Procedures for Handling Missing, Unused, and Spurious Data

No imputation of values for missing data will be performed, except as specified. Data from subjects lost to follow-up will be included in statistical analyses to the point of their last evaluation.

12.0 STUDY DURATION AND TERMINATION

The expected study duration is approximately 26 months including 18 months for completing enrollment and approximately 8 months follow-up before the primary analyses. The study started in Q1 2017. Based on DMC recommendation after futility analyses, enrolment was stopped in September 2018. Follow up for the primary analyses will be stopped in Q3 2019 or when the last subject is off study.

13.0 STUDY COMPLIANCE AND ETHICAL CONSIDERATIONS

13.1 Compliance Statement

The study will be conducted in accordance with the ICH GCP guidelines; US Title 21 CFR Parts 11, 50, 54, 56, and 312; the EU Clinical Trials Directive and its successor; principles enunciated in the Declaration of Helsinki; and all human clinical research regulations in countries where the study is conducted.

13.2 Informed Consent

The ICFs used for the study must comply with the principles of the Declaration of Helsinki, federal regulations US 21 CFR Part 50, and ICH GCP guidelines and any other local regulations. The investigator, or a person delegated by the investigator, must explain the medical aspects of the study, including the nature of the study and the treatment, orally and in writing, in such a manner that the subject is aware of potential benefits and risks. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Subjects, or a legal guardian if the subject is unable to, must give informed consent in writing.

The informed consent process must be conducted, documented in the subject’s source document (including the date), and the informed consent form must be signed and dated, before the subject undergoes any study-specific procedures.

13.3 Institutional Review Board or Independent Ethics Committee (IRB/IEC)

The investigator must submit the protocol, protocol amendments, and the ICF for the proposed study, along with any other documents required by the center's IRB/IEC to the center's duly constituted IRB/IEC for review and approval. The investigator must also ensure that the IRB/IEC reviews the progress of the study on a regular basis and, if necessary, renews its approval of the study on an annual basis. A copy of each IRB/IEC approval letter must be forwarded to the sponsor before the study is implemented. Documentation of subsequent reviews of the study must also be forwarded to the sponsor.

14.0 ADMINISTRATIVE PROCEDURES

14.1 Sponsor Responsibilities

Astex Pharmaceuticals reserves the right to terminate the study and remove all study materials from a study center at any time. Astex Pharmaceuticals and the investigators will assure that adequate consideration is given to the protection of the subjects' interests. Specific circumstances that may precipitate such termination are:

- Request by Health Authority to terminate the study.
- Unsatisfactory subject enrollment with regard to quality or quantity.
- Significant or numerous deviations from study protocol requirements, such as failures to perform required evaluations on subjects, maintain adequate study records or inaccurate, incomplete or late data recording on a recurrent basis.
- The incidence or severity of AEs in this or other studies indicating a potential health hazard caused by the study treatment.

14.1.1 Study Supplies

Refer to the Study Procedures Manual for sponsor-provided supplies for this study.

14.1.2 Investigator Training

All study centers will have a center-specific study initiation meeting to ensure the center staff understand the protocol, study requirements, and data capture processes. This training will take place before the first subject is enrolled. Each study center will be provided with information regarding GCP and regulations specific to the conduct of clinical studies. Each center is responsible for ensuring that new team members are adequately trained and the training is documented.

14.1.3 Ongoing Communication of Safety Information During the Study

The sponsor will provide the investigator with documentation of SAEs, from this study and other studies, that are related to Astex IMP and unexpected (see Section 10.3.1), as appropriate. The investigator must forward this documentation to the IRB/IEC, as described in Section 10.3.1.

The sponsor will also notify the investigator about any other significant safety findings that could alter the safety profile of the IMP from what is described in the protocol and significantly affect the safety of subjects, affect the conduct of the study, or alter the IRB/IEC's opinion about continuation of the study. This does not include safety issues that could be mitigated by simple changes in the protocol decided by the DMC (Section 4.4) such as limiting some of the eligibility criteria or reducing the IMP dose or dosing schedule.

14.1.4 Study Monitoring

Representatives of Astex Pharmaceuticals will monitor the study. Routine monitoring visits will be conducted to:

- Assure compliance with the study protocol and appropriate regulations.
- Verify that (1) the informed consent process was conducted before initiation of any study-specific procedures (ie, performed solely for the purpose of determining eligibility for the study) and before provision of study treatment, and (2) this process is adequately documented.
- Verify that the protocol, protocol amendments, and safety information are submitted to the IRB/IECs and approved by the IRB/IECs in a timely manner.
- Review the CRF/eCRFs and source documents to ensure that reported study data are accurate, complete, and verifiable from source documents.
- Verify that study treatments are stored properly and under the proper conditions, that they are in sufficient supply, and that receipt, use, and return of guadecitabine at the study centers are controlled and documented adequately.
- Verify that the investigator and study center personnel remain adequately qualified throughout the study.
- Verify that the research facilities, including laboratories and equipment, are maintained adequately to safely and properly conduct the study.

14.1.5 Study Assessment of Protocol Deviations and Prohibition of Waivers

Representatives of Astex Pharmaceuticals will assess protocol deviations to determine whether any deviation should be reported to regulatory authorities as a serious breach of GCP and the protocol. No protocol waivers will be granted.

14.1.6 Study Auditing and Inspecting

The sponsor may audit the study conduct, compliance with the protocol and accuracy of the data in one or more centers.

The investigator(s)/institution(s) will permit study-related monitoring, audits, and inspections by the sponsor, IRB/IEC, government regulatory bodies and Astex Pharmaceuticals Quality Assurance personnel or its designees by providing direct access to source data/documents after appropriate notification from sponsor.

14.2 Investigator Responsibilities

14.2.1 Subject Screening Log

The investigator must keep a record that lists all subjects who signed an informed consent and the reason for non-inclusion if they were not ultimately randomized or treated.

14.2.2 Drug Accountability

An initial supply of guadecitabine will be shipped to each study center's pharmacy when all the initiation documents, including IRB/IEC approvals, IRB/IEC approved ICF, and business agreements, have been received and reviewed by Astex Pharmaceuticals and upon activation of the study center by Astex Pharmaceuticals. Thereafter, the study pharmacist is responsible for ordering a resupply.

Keep all supplied study drug in a locked, limited-access room. The study treatment must not be used outside the context of the protocol. Under no circumstances should the investigator or other study center personnel supply any study drug to other investigators, subjects, or clinics or allow supplies to be used other than as directed by this protocol without prior authorization from Astex Pharmaceuticals.

The monitor will regularly review and verify all study treatment supplies and associated documentation.

Maintain an accurate accounting of the study treatments. These records must show dates, lot numbers, quantities received, dispensed, and returned and must be available for monitoring by the sponsor. The investigator will ensure that any used and unused supplied study drug and other study material is destroyed or returned to the sponsor on completion of the study. If the supplied study drug is destroyed at the study center, there should be documentation of destruction at the study center. The sponsor and/or their representatives will verify final drug accountability. Supplied study treatment accountability records must be maintained and readily available for inspection by representatives of Astex Pharmaceuticals and are open to inspections by regulatory authorities at any time.

14.2.3 Reporting and Recording of Study Data

Data will be captured and compiled using procedures developed by the sponsor or their representatives. Clearly record all requested study data on the CRF/eCRF and other study forms as required. Whenever possible, record the reason for missing data in the source document. Only individuals who are identified on the study personnel responsibility/signature log may enter or correct data in the CRF/eCRF. Incomplete or inconsistent data on the CRF/eCRFs will result in data queries that require resolution by the investigator or designee.

The investigator must assure subject anonymity and protection of identities from unauthorized parties. On CRF/eCRFs or other documents or subject records provided to Astex Pharmaceuticals,

identify subjects by code (subject number, initials, date of birth) and not by names. The principal investigator should maintain documents not for submission to Astex Pharmaceuticals, (eg, subjects' signed informed consent) in strict confidence.

14.2.4 Source Documentation

The investigator must maintain adequate and accurate source documents upon which CRF/eCRFs for each subject are based. They are to be separate and distinct from CRF/eCRFs, except for cases in which the sponsor has predetermined that direct data entry into specified pages of the subject's CRF/eCRF is appropriate. These records should include detailed notes on:

- The oral and written communication with the subject regarding the study treatment (including the risks and benefits of the study). Record the date of informed consent in the source documentation.
- The subject's medical history before participation in the study.
- The subject's basic identifying information, such as demographics, that links the subject's source documents with the CRF/eCRFs.
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject.
- The subject's exposure to study treatment.
- All AEs.
- The subject's exposure to any concomitant therapy (including start and stop dates, route of administration, and dosage).
- All relevant observations and data on the condition of the subject throughout the study.

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14.2.6 Records Retention

The investigator must ensure that clinical study records are retained according to national regulations, as documented in the clinical trial agreement entered into with the sponsor in

connection with this study. The investigator will maintain all records and documents pertaining to the study including, but not limited to, those outlined above (see Section 14.2.4) for a period of: at least 2 years after FDA approval of the drug or at least 2 years after withdrawal of the IND under which this study was conducted, whichever is longer. In countries outside the US, records must be kept for the period of time required by the US FDA as a minimum, and record retention should also comply with the local country regulatory requirements, if longer retention times are required than in the US. Mandatory documentation includes copies of study protocols and amendments, financial disclosures, each FDA Form 1572, IRB/IEC approval letters, signed ICFs, drug accountability records, SAE forms transmitted to Astex Pharmaceuticals, subject files (source documentation) that substantiate entries in CRF/eCRFs, all relevant correspondence, and other documents pertaining to the conduct of the study. These records must remain in each subject's study file and be available for verification by study monitors at any time.

The investigator must inform the sponsor immediately if any documents are to be destroyed, transferred to a different facility, or transferred to a different owner. The sponsor should be given the option of collecting the documents before destruction.

14.3 Clinical Trial Insurance

Clinical trial insurance has been undertaken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating study centers upon request.

14.4 Study Administrative Letters and Protocol Amendments

Astex Pharmaceuticals may issue Study Administrative Letters (1) to clarify certain statements or correct obvious errors/typos/inconsistencies in the study protocol, (2) to change the logistical or administrative aspects of the study, such as study personnel or contact information, or (3) to instruct investigators of DMC safety decisions for immediate implementation for safety reasons (Section 4.4).

For all other changes, Astex Pharmaceuticals will initiate any change to the protocol in a protocol amendment document and seek approval from relevant regulatory authorities before implementation where applicable. The study center will submit the amendment to the IRB/IEC together with, if applicable, a revised model ICF. If the change in any way increases the risk to the subject, information on the increased risk must be provided to subjects already actively participating in the study, and they must read, understand and sign any revised ICF confirming willingness to remain in the study.

The investigator must obtain IRB/IEC approval before any protocol amendment can be implemented, except for administrative changes or changes necessary to eliminate an immediate risk to study subjects, as outlined above.

15.0 POLICY FOR PUBLICATION AND PRESENTATION OF DATA

The sponsor encourages the scientific publication of data from clinical research studies. However, investigators may not present or publish partial or complete study results individually without review by the sponsor. The principal investigators and the sponsor may propose appropriate scientific manuscripts or abstracts from the study data. The sponsor must review and comment on all proposed publications before submission for publication. The detailed procedures for the review of publications are set out in the clinical trial agreement entered into with the sponsor in connection with this study. These procedures are in place to ensure coordination of study data publication and adequate review of data for publication against the validated study database for accuracy. Names of all investigators and sponsor representatives responsible for designing the study and analyzing the results will be included in the publication(s).

Qualification of authorship will follow the requirements of the International Committee of Medical Journal Editors (www.icmje.org). In most cases, the principal investigators at the centers with the highest participation in the study shall be listed as lead authors on manuscripts and reports of study results. In addition, other than clinical pharmacology studies in healthy volunteers or Phase 1 studies, all clinical studies must be registered with ClinicalTrials.gov.

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17.0 APPENDICES

APPENDIX 1: ECOG PERFORMANCE STATUS

Score	ECOG Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: ECOG Performance Status — http://www.ecog.org/general/perf_stat.html (accessed 16 August 2016)

APPENDIX 2: QUALITY OF LIFE EQ-5D-5L SAMPLE

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

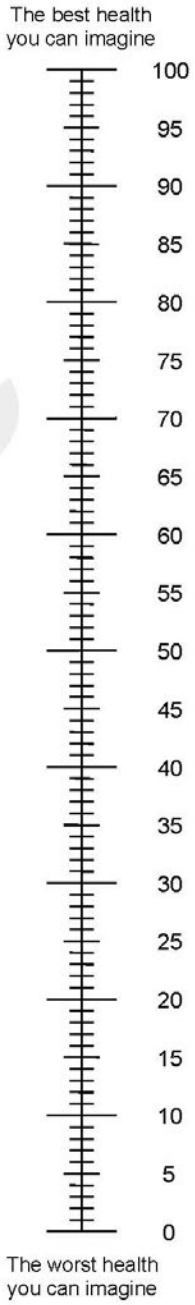
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX 3: CYTOGENETICS-BASED RISK CLASSIFICATION

Cytogenetics-based risk classification is based on National Comprehensive Cancer Network (NCCN) Guidelines® (2014) as follows:

Risk Status Based on Cytogenetics[a]

Risk Status	Cytogenetics
Better-risk	inv(16)[b,c] or t(16;16)[b] t(8;21)[b] t(15;17)
Intermediate-risk	Normal cytogenetics +8 alone t(9;11) Other non-defined
Poor-risk	Complex (≥3 clonal chromosomal abnormalities) Monosomal karyotype -5, 5q-, -7, 7q- 11q23 - non t(9;11) inv(3), t(3;3) t(6;9) t(9;22)[d]

[a] The molecular abnormalities included in this table reflect those for which validated assays are available in standardized commercial laboratories. Given the rapidly evolving field, risk stratification should be modified based on continuous evaluation of research data. Other novel genetic mutations have been identified that may have prognostic significance.

[b] Other cytogenetic abnormalities in addition to these findings do not alter better risk status.

[c] Paschka P, Du J, Schlenk RF, et al. Secondary genetic lesions in acute myeloid leukemia with inv(16) or t(16;16): a study of the German-Austrian AML study group (AMLSG). Blood 2013;121:170-177.

[d] For Philadelphia+ AML t(9;22), manage as myeloid blast crisis in chronic myeloid leukemia, with addition of tyrosine kinase inhibitors.

Sources: NCCN Guidelines: Acute Myeloid Leukemia. Version.2. 2014. NCCN.org

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