16.1.1 Protocol and Protocol Amendments

Protocol Amendment 4.0 Global (02 October 2018)

- Summary of Changes – Amendment 4.0 Global (02 October 2018)
- Summary of Changes – Amendment 3.0 Global (15 February 2018)
- Summary of Changes – Amendment 2.0 Global (19 September 2017)
- Summary of Changes – Amendment 1.1 UK / France (14 March 2017)
- Summary of Changes – Amendment 1.0 (19 September 2016)

Clinical Study Protocol — SGI-110-07

A Phase 3, Multicenter, Randomized, Open-Label Study of Guadecitabine (SGI-110) versus Treatment Choice in Adults with Myelodysplastic Syndromes (MDS) or Chronic Myelomonocytic Leukemia (CMML) Previously Treated with Hypomethylating Agents

PROTOCOL TITLE PAGE

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

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Study Acknowledgement

A Phase 3, Multicenter, Randomized, Open-Label Study of Guadecitabine (SGI-110) versus Treatment Choice in Adults with Myelodysplastic Syndromes (MDS) or Chronic Myelomonocytic Leukemia (CMML) Previously Treated with Hypomethylating Agents

Version 5.0 (Amendment 4), 02 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 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

A Phase 3, Multicenter, Randomized, Open-Label Study of Guadecitabine (SGI-110) versus Treatment Choice in Adults with Myelodysplastic Syndromes (MDS) or Chronic Myelomonocytic Leukemia (CMML) Previously Treated with Hypomethylating Agents

Version 5.0 (Amendment 4), 02 October 2018

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PROTOCOL APPROVAL PAGE

A Phase 3, Multicenter, Randomized, Open-Label Study of Guadecitabine (SGI-110) versus Treatment Choice in Adults with Myelodysplastic Syndromes (MDS) or Chronic Myelomonocytic Leukemia (CMML) Previously Treated with Hypomethylating Agents

Version 5.0 (Amendment 4), 02 October 2018

QA APPROVAL

Quality Assurance and Compliance

[redacted]

APPROVED BY

Vice President, Global Regulatory Affairs

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President and Chief Medical Officer

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PROTOCOL SYNOPSIS

Study Number and Title:

SGI-110-07: A Phase 3, Multicenter, Randomized, Open-Label Study of Guadecitabine (SGI-110) versus Treatment Choice in Adults with Myelodysplastic Syndromes (MDS) or Chronic Myelomonocytic Leukemia (CMML) Previously Treated with Hypomethylating Agents

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

Clinical Phase: 3

Study Centers Planned/Country: Multicenter global study (approximately 100 centers in 15 countries)

Study Objective(s):

Primary Objective

- To assess and compare overall survival (OS) between guadecitabine and treatment choice (TC) in adults with MDS or CMML previously treated with a hypomethylating agent (azacitidine or decitabine, or both).

Secondary Objectives

To assess and compare effects of guadecitabine and TC in adults with MDS or CMML previously treated with a hypomethylating agent (azacitidine or decitabine, or both) with respect to the following variables:

- Transfusion independence.
- Marrow complete response (mCR) with transfusion independence.
- Survival rate at 1 year after randomization.
- Leukemia-free survival.
- Number of days alive and out of the hospital (NDAOH).
- Disease response based on IWG 2006 MDS criteria including complete response (CR), partial response (PR), mCR, and hematological improvement (HI; erythroid, platelet, or neutrophil response); and duration of response.
- Number of red blood cell (RBC) and platelet transfusions.
- 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 408 subjects will be randomly assigned to either guadecitabine or TC in a 2:1 ratio.

- Guadecitabine: approximately 272 subjects.
- TC: approximately 136 subjects.

  Before randomization, the investigator will assign each subject to one of the following TC options:
  - Low dose cytarabine (LDAC).
  - Standard Intensive Chemotherapy (IC) of a 7+3 regimen.
  - Best Supportive Care (BSC) only.

Best Supportive Care will be provided to all subjects as per standard and institutional practice. Subjects randomized to TC will not be 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 disease category (MDS vs CMML), bone marrow (BM) blasts (BM blasts >10% vs BM blasts ≤10%), TC option (LDAC vs IC vs BSC), and study center region (North America vs the rest of the world [ROW]).

Study Population:
Approximately 408 adults previously treated for MDS or CMML.

Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria.

1. Adult subjects ≥18 years of age who are able to understand and comply with study procedures, and provide written informed consent before any study-specific procedure.
2. Cytologically or histologically confirmed diagnosis of MDS or CMML according to the 2008 World Health Organization (WHO) classification.
3. Performance status (Eastern Cooperative Oncology Group [ECOG]) of 0-2.
4. Subjects with previously treated MDS or CMML, defined as prior treatment with at least one hypomethylating agent (HMA; azacitidine and/or decitabine) for intermediate or high risk MDS or CMML whose disease progressed, relapsed, or was refractory to HMA treatment as follows:
    a. Subject received HMA for at least 6 cycles and is transfusion dependent (as defined in 5b below), OR
    b. Subject received HMA for at least 2 complete cycles and had disease progression defined as
        i. ≥50% increase in bone marrow blasts from pre-HMA-treatment levels or from nadir post-HMA-treatment levels to >5% (for subjects with pretreatment or nadir blasts ≤5%) or to >10% (for subjects with pretreatment or nadir blasts >5%), and/or
        ii. Transfusion dependent and ≥2 g/dL reduction of Hgb from pre-HMA-treatment levels.

    In addition to HMAs, other prior treatments for MDS such as lenalidomide, cytarabine, intensive chemotherapy, hydroxyurea, erythropoietin and other growth factors, or hematopoietic cell transplant (HCT) are allowed.
5. Subjects must have either:
    a. Bone marrow blasts >5% at randomization, OR
    b. Transfusion dependence, defined as having had transfusion (in the setting of active disease) of 2 or more units of RBC or platelets within 8 weeks prior to randomization.
6. Creatinine clearance or glomerular filtration rate ≥30 mL/min 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 childbearing potential must not be pregnant or breastfeeding and must have a negative pregnancy test at screening. Women of childbearing potential and men with female partners of childbearing 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 and for at least 3 months after completing treatment and (b) while receiving treatment with LDAC or IC and for at least 6 months after completing treatment or for the duration specified in local prescribing information, whichever is longer.

Exclusion Criteria

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

1. Subjects who have been diagnosed as having acute myeloid leukemia (AML) with peripheral blood or bone marrow blasts of ≥20%.
2. Subjects who may still be sensitive to repeated treatment with decitabine or azacitidine such as subjects who had response to prior decitabine or azacitidine treatment, but relapsed >6 months after stopping treatment with these agents.
3. Prior treatment with guadecitabine.
4. Hypersensitivity to decitabine, guadecitabine, or any of their excipients.
5. Second malignancy currently requiring active therapy, except breast or prostate cancer stable on or responding to endocrine therapy.
6. Treated with any investigational drug within 2 weeks of the first dose of study treatment.
7. Total serum bilirubin >2.5 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.
8. 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.
9. 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.

10. Refractory congestive heart failure unresponsive to medical treatment, active infection resistant to all antibiotics, or advanced non-MDS associated pulmonary disease requiring >2 liters per minute (LPM) oxygen.
11. Life expectancy of less than one month.
12. Subjects with TP53 mutation.

Study Treatment:

Guadecitabine: 60 mg/m^2 given SC daily on Days 1-5 in 28-day cycles (delayed as needed to allow blood count recovery). 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. BSC should be given according to standard and institutional practice.

Treatment Choice (TC): Before randomization, the investigator will assign each subject to one of the following TC options:

- Low dose cytarabine (LDAC) given as 20 mg/m^2 SC or IV once daily for 14 days in 28-day cycles (delayed as needed to allow blood count recovery). Other schedules (eg, BID dosing) are allowed if within institutional and standard practices. Treatment should be given for at least 4 cycles in the absence of disease progression or unacceptable toxicity. Subjects who are responding or have stable disease should continue treatment as per standard and institutional practice. BSC should be given as per institutional and standard practice.
- Standard Intensive Chemotherapy (IC) of a 7+3 regimen: given as cytarabine 100-200 mg/m^2/day given as continuous infusion for 7 days and an anthracycline given as per institutional standard practice such as daunorubicin (45-60 mg/m^2/day), or idarubicin (9-12 mg/m^2/day), or mitoxantrone (8-12 mg/m^2/day) by intravenous infusion for 3 days. Subjects who achieve complete or partial response after IC induction should receive at least one or more cycles with reduced cytotoxic doses followed by BSC as per standard and institutional practice.
- Best Supportive Care (BSC) only: given according to standard and institutional practice. BSC includes, but is not limited to blood transfusions (RBCs or platelets), growth factors including erythropoiesis stimulating agents (ESA), granulocyte stimulating factors (GSFs), iron chelating therapy, and broad spectrum antibiotics and/or antifungals.

Study Endpoints:

Primary Endpoint(s)

- Overall Survival (OS), defined as the number of days from the day the subject was randomized to the date of death (regardless of cause).

Secondary Endpoint(s)

- Transfusion independence for any 8 consecutive weeks based on rolling 8-week assessments. Number and rate of subjects who are free of transfusions for 8 consecutive weeks (or more) at any time after start of study treatment and who have Hgb of ≥8 g/dL and platelets ≥20×10^9/L.
- Marrow CR (mCR) based on IWG 2006 criteria with transfusion independence (as defined above).
- Survival rate at 1 year after randomization.
- Leukemia-free survival defined as the number of days from the day of randomization to the date when BM or peripheral blood (PB) blasts reach ≥20%, or death of any cause.
- Number of days alive and out of the hospital (NDAOH).
- Disease response including CR, mCR, PR, and HI; including HI with erythroid (HI-E), neutrophil (HI-N), or platelet (HI-P) response, based on IWG 2006 criteria.
- Duration of response.
- Number of RBC or platelet transfusions (units) over the duration of the study treatment.
- Health-related QOL by EQ-5D™ (consisting of the EQ-5D-5L descriptive system and the EQ Visual Analogue Scale [EQ VAS]).
- Incidence and severity of adverse events (AEs).
- 30- and 60-day all-cause mortality.

Study Assessments and Procedures:

A 21-day screening period is allowed (unless otherwise specified). After randomization, visits will occur on every treatment day. In addition, visits will occur on Days 8, 15, and 22 of the first 2 cycles of therapy, and on Days 1 and 15 of Cycles 3-6. (Days 8, 15, and 22 are not required for subjects receiving TC; instead institutional standards should be followed.) In Cycles >6, only treatment day visits are required, 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. 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 2 months thereafter. For subjects who discontinue study treatment after Cycle 6, long-term follow-up will be every 2 months.

Efficacy Assessments:

Survival will be monitored and documented throughout the study.

Transfusion (blood and platelet) requirements will be recorded every month during the first 6 months and then every 2 months thereafter. All hospital admissions will be documented and used to determine NDAOH.

Peripheral blood (PB) and bone marrow (BM) aspirate or biopsy (including touch prep slides as specified in the schedule of events) will be collected and used for response assessments. BM aspirate or biopsy will be performed at screening and at the end of Cycles 2, 4, and 6. Subjects treated with standard IC may have an additional BM aspirate or biopsy after the first cycle of induction in addition or instead of the end of Cycle 2 BM assessment. After Cycle 6, BM assessment (BM aspirate or biopsy) will be repeated every 4 months until PB or BM assessment shows disease progression or relapse.

[redacted]

Health-related QOL Assessment:

QOL will be assessed using EQ-5D before treatment on Day 1 of each cycle for the first 6 cycles (or monthly until 6 months after the start of study treatment for subjects who discontinue treatment before 6 cycles).

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).

Sample Size and Statistical Analyses

Sample Size Calculation:

In order to provide power of at least 89% to detect a difference in hazard ratio of approximately 0.68 (median OS of 6 months for the TC control arm and 8.8 months for the guadecitabine arm) using a 2-sided stratified log-rank test at an overall 2-sided 0.05 alpha level, given the use of a 2:1 randomization, the trial will require 316 death events. Assuming accrual is uniform over an 18-month enrollment period with an additional follow-up of 9 months, approximately 408 subjects will need to be randomized. If, after a follow-up of 12 months from the last subject randomized, the 316 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. If at 12 months 277 deaths events have not been observed, the primary analysis will be conducted when 277 death events have been observed (corresponding to 85% power).

Efficacy:

The primary endpoint of OS will be displayed using Kaplan-Meier estimates and will be compared between the 2 treatment groups (guadecitabine and TC) 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 alpha error rate at 0.05 (2-sided), the nominal alpha to be used in the final analysis will be calculated accounting for the unspent alpha at the interim analysis.

If statistical significance is achieved for OS, then, hierarchically the 8-week transfusion independence, mCR with transfusion independence, 1-year survival rate, leukemia-free survival, and NDAOH will be compared between the 2 treatment groups. The 8-week transfusion independence and mCR will be compared between the 2 treatment groups using a Cochran Mantel-Haenszel test. The 1-year survival rate will be compared using Kaplan-Meier estimates and standard errors estimated by Greenwood formula. Leukemia-free survival will be estimated by Kaplan-Meier procedure and compared by stratified log-rank test. 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 clinical laboratory tests (hematology and chemistry), concomitant medications, physical examination, vital signs, ECOG performance status, 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) version 4.03. 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 (Cycle 1 Day 1) divided by the total number of subjects included in the safety dataset.

Interim Analysis:

One interim analysis of OS is planned with a 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 316 death events. The interim analysis will be conducted by an independent DMC after approximately half of the required death events have occurred. 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 and Termination:

The expected study duration is approximately 27 months including 18 months for completing enrollment and approximately 9 months (based on the anticipated number of death events) for follow-up before final analysis. The study is expected to start in Q4 2016 and end in Q1 2019.

Compliance Statement:

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guideline, 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

ADL	activities of daily living
AE	adverse event
allo-HSCT	allogeneic hematopoietic stem cell transplant
AML	acute myeloid leukemia
AUC	area under the curve
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	Cockroft-Gault
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum concentration
CMML	chronic myelomonocytic leukemia
CR	complete response
CRc	composite complete response (CR+CRi+CRp)
CRi	complete response with incomplete blood count recovery
CRp	complete response with incomplete platelet recovery
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EMEA	European Agency for the Evaluation of Medicinal Products
ESA	erythropoiesis stimulating agents
EQ VAS	EQ visual analog scale
EQ-5D-5L	EQ-5D 5 level health questionnaire
FAB	French-American-British
FIH	first-in-human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GSF	granulocyte stimulating factor
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HCT	hematopoietic cell transplant
HI	hematological improvement
HI-E	HI with erythroid response
HI-N	HI with neutrophil response
HI-P	HI with platelet response
HIV	human immunodeficiency virus
HMA	hypomethylating agent
HNSTD	highest non-severely toxic dose
IB	Investigator Brochure
IC	intensive chemotherapy

ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product (the specific Astex drug product under study)
Int-1	IPSS risk group intermediate-1
Int-2	IPSS risk group intermediate-2
IPSS	International Prognostic Scoring System
IPSS-R	revised IPSS
IRB	Institutional Review Board
IV	intravenous
IWG	International Working Group
LDAC	low-dose cytarabine
LINE-1	long interspersed nucleotide element-1
LPM	liters per minute
LTFU	long-term follow-up
mCR	marrow complete response
MDS	myelodysplastic syndromes
MDS/MPN	myelodysplastic/myeloproliferative neoplasm
MDRD	Modification of Diet in Renal Disease
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 the hospital
NOAEL	no observed adverse event level
OS	overall survival
OSHA	Occupational Safety and Health Administration
PB	peripheral blood
PD	pharmacodynamic(s)
[redacted]	[redacted]
PR	partial response
PT	preferred term
QOL	quality of life
QT	QT interval
QTc	heart rate corrected interval
r/r	relapsed or refractory
RBC	red blood cell
ROW	rest of world
SAE	serious adverse event
SC	subcutaneous
SEER	Surveillance, Epidemiology and End Results
SOC	system organ class
SSC	Study Steering Committee
STD_{10}	dose severely toxic to 10% of animals/rodents
SUSAR	suspected unexpected serious adverse reactions
TC	treatment choice
TK	toxicokinetic
TN	treatment-naïve
ULN	upper limit of normal
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

Myelodysplastic syndromes (MDS) are a heterogeneous group of hematopoietic stem cell disorders characterized by dysplastic changes in myeloid, erythroid, and megakaryocytic progenitors. This group of diseases clinically presents with and associated with cytopenias affecting one or more of the three lineages and may progress to acute myeloid leukemia (AML) (Bennett et al 1982; Cheson et al 2000; Heaney and Golde 1999; Silverman 2003). While MDS is relatively uncommon in the general population, the incidence increases with age, hence disease management is often complicated by the presence of non-malignant co-morbidities and lessened ability to tolerate intensive treatment.

Diagnosis and classification of MDS has evolved based on new scientific and clinical information, notably improved genetic analysis. All classification systems require comprehensive evaluation of peripheral smear and cell counts, bone marrow morphology, clinical course, and knowledge of ongoing medical conditions and medications as these may cause changes in some lineages.

The older French-American-British (FAB) classification (Bennett et al 1982) required diagnostic changes in at least two lineages and defined a spectrum of progressively worse prognosis patients based primarily on blasts with >30% marrow blasts defined as AML. In this paradigm, MDS is rather indolent with median survival being approximately 3 to 6 years for patients with refractory anemia (<5% marrow blasts). Patients with chronic myelomonocytic leukemia (CMML) were also included as a category of MDS, thus the initial agents approved for treatment of MDS (azacitidine and decitabine) included CMML. The most current MDS classification (2008 WHO Classification) defines 7 different MDS groups and separately describes CMML as a myelodysplastic/myeloproliferative neoplasm (MDS/MPN) (Vardiman et al 2009) though treatment and approach is essentially the same as for MDS.

CMML is a clonal hematologic malignancy characterized by an absolute peripheral monocytosis, ineffective hemopoiesis, splenomegaly, and an increased risk of transformation to AML. The median age at diagnosis is 65 to 75 years, with disease predominance in males. Prognosis is generally poor, with a median survival of 12 to 19 months (Padron et al 2014). Genetic studies have also shown that CMML has a distinct pattern of associated genetic abnormalities (Meggendorfer et al 2012).

The incidence of MDS and CMML increases with age and is more prevalent in white men (Ma 2012; Howlader et al 2016). MDS is estimated to occur in 4.8 of every 100,000 Americans, yielding an incidence rate of about 13,000 new cases each year (ACS 2015 Key MDS Statistics); however, some researchers believe that the incidence is significantly underestimated (Cogle 2015; Craig et al 2012; Cogle et al 2011).

According to the most recent SEER Cancer Statistics (2016), the incidence rate of MDS increases substantially in older populations (Howlader et al 2016). For example, in those under 40 years of age at diagnosis, the age-adjusted (age-adjusted to the 2000 US Std Population) incidence rate of MDS is only 0.1 per 100,000 people, but for individuals aged 70 to 79 and over 80, the incidence rate rises to 30.2 and 59.8 per 100,000, respectively. While the rate of individuals in the US diagnosed with CMML is lower than those diagnosed with MDS, the incidence rate of individuals diagnosed with CMML also increases with age. In individuals aged 40 to 49 years at the time of CMML diagnosis, the incidence rate is 0.1 per 100,000 people and for individuals aged 70 to 79 years and over 80 years the rate is 3.0 and 4.7 per 100,000 people, respectively. Only 19 cases of CMML were reported in individuals under 40 years of age during the reporting period (2009-2015). Given this pattern, it is not surprising that MDS/CMML occurs predominantly in persons 60 years of age and older and it is likely that the incidence of MDS/CMML will continue to rise in conjunction with our aging population.

Similar incidence rates have been reported in Europe. The incidence of MDS in Europe is estimated to occur in 4 of every 100,000 persons. In patients ≥70 years of age, the incidence rises to 40 to 50 cases in every 100,000 people (Neukirchen et al 2011).

Patients often present with complications related to anemia (fatigue), neutropenia (infections), or thrombocytopenia (bleeding/bruising). In addition, variable blast expansion, and, less commonly, leukocytosis are observed. About one-third of MDS patients develop AML. Patients die either from complications associated with cytopenias (infections and bleeding) or from transformation to AML. In practice, "lower risk" MDS patients may be distinguished from "higher risk" MDS patients by their degree of pre-leukemic blast expansion, responses to therapeutic agents, disease outcomes, and prognosis (Bejanyan and Sekeres 2011). These factors have allowed the establishment of an International Prognostic Scoring System (IPSS) to predict survival and progression to AML (Greenberg et al 1997) as well as aiding treatment decisions. The IPSS rates 3 factors: percentage of blasts in bone marrow (<5%, 5%-10%, 11%-20%, 21%-30%), karyotype/chromosome abnormalities (normal, Y-, 5q-, 20q-; abnormal chromosome 7 or ≥3 abnormalities; all other cytogenic abnormalities), and blood counts (no cytopenia or cytopenia of 1 cell type; cytopenia of 2 or 3 cell types). The scores for each factor are added to make the IPSS score, with the lowest score having the best outlook. The IPSS groups patients with MDS into 4 risk groups: low risk, intermediate-1 risk (Int-1), intermediate-2 risk (Int-2), or high risk.

Survival varies by type of MDS risk classification at initial diagnosis. Using the IPSS risk classification system median survival is 5.7 years for low risk, 3.5 years for Int-1 risk, 1.1 years for Int-2 risk, and 0.4 years for high risk (Greenberg et al 1997). While there are a variety of different prognostic systems that may be used or are being investigated (eg, revised IPSS

[IPSS-R]), IPSS is the standard prognostic system. In a recent study investigating several different prognostic systems (Greenberg et al 2012), an analysis of the IPSS scoring system showed patients with lower risk (IPSS low risk or Int-1) MDS (77% of patients) had an expected median survival of 3.6 to 7 years. Median survival for higher risk patients (Int-2 and high-risk MDS) ranged from 0.9 to 1.5 years. The IPSS prognostic system is generally used at first diagnosis and has not been shown to be relevant for prognosis in patients with recurrent disease or who fail to respond (Bejanyan and Sekeres 2011).

1.2 Treatment Options

MDS is a complex, life threatening disorder in which treatment strategies are equally complicated by age, type of MDS, and risk stratification. Although newer treatment options provide hope beyond supportive care, there is still ambiguity among healthcare providers on which strategies to use on which patient. A number of MDS patients will progress to AML, a more aggressive cancer with a reduced survival rate.

All patients with MDS and CMML receive supportive care (eg, growth factors, blood or platelet transfusions, antibiotics, antifungals). High-dose chemotherapy with stem cell/bone marrow transplant is the only potentially curative treatment. However, most patients are not candidates (older patients or patients who have other medical problems) for a higher-risk treatment such as stem cell transplant. For some older patients, allogenic stem cell transplant may be an option following lower intensity treatment. The intensity of treatment (chemotherapy including hypomethylating agents [HMAs]) and ability to undergo stem cell transplant is largely based on risk factors. A combination of these therapies is often used. However, with the discovery and use of treatments such as azacitidine, decitabine, and lenalidomide, the treatment paradigm for MDS has been transformed (Bejar and Steensma 2014).

Two HMAs have been approved in most countries for the treatment of intermediate and high risk MDS and CMML: azacitidine and decitabine. These agents have dramatically changed the course of treatment for MDS and have improved the outcome of patients who previously had very poor survival. Patients administered azacitidine at a subcutaneous dose of 75 mg/m^2 once daily for 7 days (Daily×7) showed an overall response rate (complete response [CR] + partial response [PR]) of 15.7%, which was significantly greater than the response rate of 0% in the observation group (p<0.0001) (Vidaza 2014). Similarly, patients with intermediate- or high-risk MDS who were administered intravenous (IV) decitabine (Dacogen®) at a dose of 20 mg/m^2 once daily for 5 days (Daily×5) showed an overall response rate of 16% (Dacogen Package Insert 2014).

The choice of optimal front-line therapy in MDS depends on accurate risk stratification (NCCN MDS 2016). The IPSS is the most common system in use. Molecular profiling has the potential to improve prognostication, risk stratification, and diagnosis (Nazha et al 2015). Lenalidomide is indicated specifically for patients with low-risk MDS and 5q chromosomal deletion (del 5q). The identification of biologically relevant pathways is anticipated to ultimately lead to more targeted therapeutic agents. Allogeneic hematopoietic stem cell transplant (allo-HSCT) is increasingly

being used in older adults with MDS, and it should be considered early in patients with higher risk disease (NCCN MDS 2016).

Treatment for CMML is similar to MDS. As with MDS, the sole disease-modifying therapy for CMML currently has been shown to be allo-HSCT. However, most CMML patients are not candidates for transplant because of advanced age and/or co-morbidities. The HMAs azacitidine and decitabine are also currently approved for the treatment of CMML in several jurisdictions.

Standard front-line treatment for MDS patients with intermediate or high risk is HMAs (azacitidine or decitabine). Patients who are candidates for stem cell transplant and have a donor available undergo transplant. Patients who do not respond to treatment with HMAs have few options and no options that have been shown to be effective or to prolong survival after failure of HMAs, though some patients have received allogeneic transplants with reasonable outcomes (Prebet et al 2011).

At present, there are no approved treatment options for MDS patients who rapidly progress on HMA therapy or who fail to respond to adequate HMA treatment. Other than hypomethylating agents, common "conventional care" regimens in MDS patients include low-dose cytarabine (LDAC), standard intensive chemotherapy (IC) of a 7+3 regimen, or best supportive care (BSC) (Fenaux et al 2009; Seymour et al 2010).

1.3 Guadecitabine

Guadecitabine is a new chemical entity that incorporates decitabine and deoxyguanosine linked by a phosphodiester bond. Unlike decitabine, guadecitabine is resistant to deamination by cytidine deaminases (CDAs). 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.

The DNA methylation inhibitors, also known as HMAs, azacitidine and decitabine, are approved in several jurisdictions for treatment of intermediate and high risk patients with MDS including CMML. Decitabine for intravenous (IV) injection (Dacogen®) is marketed in the United States (US) for the treatment of patients with intermediate or high risk MDS including CMML (Dacogen Package Insert 2014) and in the European Union for the treatment of elderly patients with AML who are not candidates for standard induction chemotherapy (Dacogen Summary of Product characteristics 2015). There is no approved treatment for patients with MDS who fail or relapse after treatment with azacitidine or decitabine.

Compared with IV decitabine, decitabine from subcutaneous (SC) guadecitabine had prolonged exposure and lower C_{max} (Issa et al 2015). This differentiated pharmacokinetic ([redacted] 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 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.

[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 (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 MDS (r/r MDS) 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 dose-limiting toxicities (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 methylation 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 relapsed/refractory 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 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 patients 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 relapsed/refractory AML subjects and then in treatment-naïve elderly AML subjects.

Relapsed/Refractory MDS

Phase 2 in the cohort of subjects with relapsed or refractory MDS is still ongoing treatment. All results presented below are based on a data cutoff of November 2015 for r/r MDS cohorts (53 patients).

Eligibility for r/r MDS subjects in Study SGI-110-01 Phase 2 is defined below.

- ≥18 years of age.
- Confirmed diagnosis of MDS including CMML.
- ECOG performance status of 0-2.
- Intermediate (Int-2) or high-risk MDS including CMML, relapsed or refractory to prior treatment.

Subjects were randomly assigned to either 60 or 90 mg/m^2/day guadecitabine Daily×5. The primary endpoint for MDS subjects was overall response rate (CR+PR+mCR+HI) as measured based on the International Working Group (IWG) 2006 MDS Response Criteria (Cheson et al 2006). AEs and LINE-1 DNA methylation pharmacodynamics were secondary endpoints for safety and biological activity.

Table 1 presents baseline characteristics for subjects with r/r MDS enrolled in Phase 2 Dose Expansion. Of the 53 subjects enrolled with r/r MDS, 26 were randomized to 60 mg/m^2 and 27 were randomized to 90 mg/m^2. The median age of subjects was 72 years and 60% of patients were men. Subject baseline characteristics were generally balanced between the 2 dose groups with some exceptions. A higher proportion of subjects with CMML were randomized to the 60 mg/m^2 group (35%) compared with the 90 mg/m^2 group (4%), and there was a lower proportion of subjects with IPSS high-risk MDS in the 60 vs 90 mg/m^2 groups (35% vs 59%, respectively). At baseline, 50% and 78% of subjects in the 60 and 90 mg/m^2 groups had bone marrow (BM) blasts >5%, respectively. Transfusion dependence at baseline was balanced between the 2 groups with 62% and 70% of patients in the 60 and 90 mg/m^2 groups, respectively being transfusion-dependent (red blood cells [RBCs] or platelets).

Table 1: Baseline Characteristics: Relapsed/Refractory MDS Subjects (Phase 2, Study SGI-110-01)

Baseline Characteristics		60 mg/m^2 Daily×5 (N=26)	90 mg/m^2 Daily×5 (N=27)	Total (N=53)
Median Age, years (range)		73 (55-85)	72 (52-89)	72 (52-89)
Gender	Men	16 (62%)	16 (59%)	32 (60%)
	Women	10 (38%)	11 (41%)	21 (40%)
ECOG Performance Status, n (%)				
0		6 (23%)	5 (19%)	11 (21%)
1		14 (54%)	17 (63%)	31 (58%)
2		6 (23%)	5 (19%)	11 (21%)
Prior Treatment[b], n (%)				
Decitabine (DAC)		6 (23%)	11 (41%)	17 (32%)
Azacitidine (AZA)		20 (77%)	21 (78%)	41 (77%)
DAC and AZA		2 (8%)	5 (19%)	7 (13%)
Median Number of Prior Regimens (range)		1 (1-4)	1 (1-4)	1 (1-4)
IPSS Classification[a]	Int-1	2 (8%)	2 (7%)	4 (8%)
	Int-2	6 (23%)	7 (26%)	13 (25%)
	High risk	9 (35%)	16 (59%)	25 (47%)
	CMML	9 (35%)	1 (4%)	10 (19%)
Time Since Prior Treatment[b]	<6 months	19 (79%)	23 (85%)	42 (82%)
	≥6 months	5 (21%)	4 (15%)	9 (18%)
Duration of Prior HMA[b]	<6 months	3 (12.5%)	8 (30%)	11 (22%)
	≥6 months	21 (87.5%)	19 (70%)	40 (78%)
Median % Blasts (range)		5.5 (0-18)	9 (1-19)	8 (0-19)
BM Blasts, n (%)	≤5%	13 (50%)	6 (22%)	19 (36%)
	>5%	13 (50%)	21 (78%)	34 (64%)
Transfusion dependent (RBCs or platelets)		16 (62%)	19 (70%)	35 (66%)

[a] IPSS classification is missing for 1 subject in the 90 mg/m^2 group.

[b] For these categories n = 24 for 60 mg/m^2, n = 27 for 90 mg/m^2, and n = 51 for total (2 patients did not receive prior HMA)

Source: Table MDS_RR_DEMO01 (13 Nov 2015), Time-Last-HMA (10 Feb 2016), Prior HMA and BM Blasts (10 Feb 2016)

The overall response (CR+mCR+HI) rate was 43.4% for all r/r MDS subjects in Phase 2 Dose Expansion (Table 2). The proportion of subjects who achieved a best response of CR and HI was similar between the dose groups. The proportion of subjects who achieved a best response of mCR was higher in the 90 mg/m^2 group compared with the 60 mg/m^2 group as more patients with >5% blasts were in the 90 mg/m^2 group (mCR cannot be designated for patients with ≤5% BM blasts).

Table 2: Response to Treatment: Relapsed/Refractory Subjects with MDS (Phase 2, Study SGI-110-01)

	Response Rate, n (%) [95% CI]		
Response Category[a]	**60 mg/m^2 Daily×5 (N=26)**	**90 mg/m^2 Daily×5 (N=27)**	**Total (N=53)**
Complete response (CR)	1 (3.8)	1 (3.7)	2 (3.8)
Marrow CR (mCR)	4 (15.4)	11 (40.7)	15 (28.3)
Hematological improvement (HI)	5 (19.2)	6 (22.2)	11 (20.8)
Overall Response (CR+mCR+HI)	**7 (26.9) [11.6-47.8]**	**16 (59.3) [38.8-77.6]**	**23 (43.4) [29.8-57.7]**

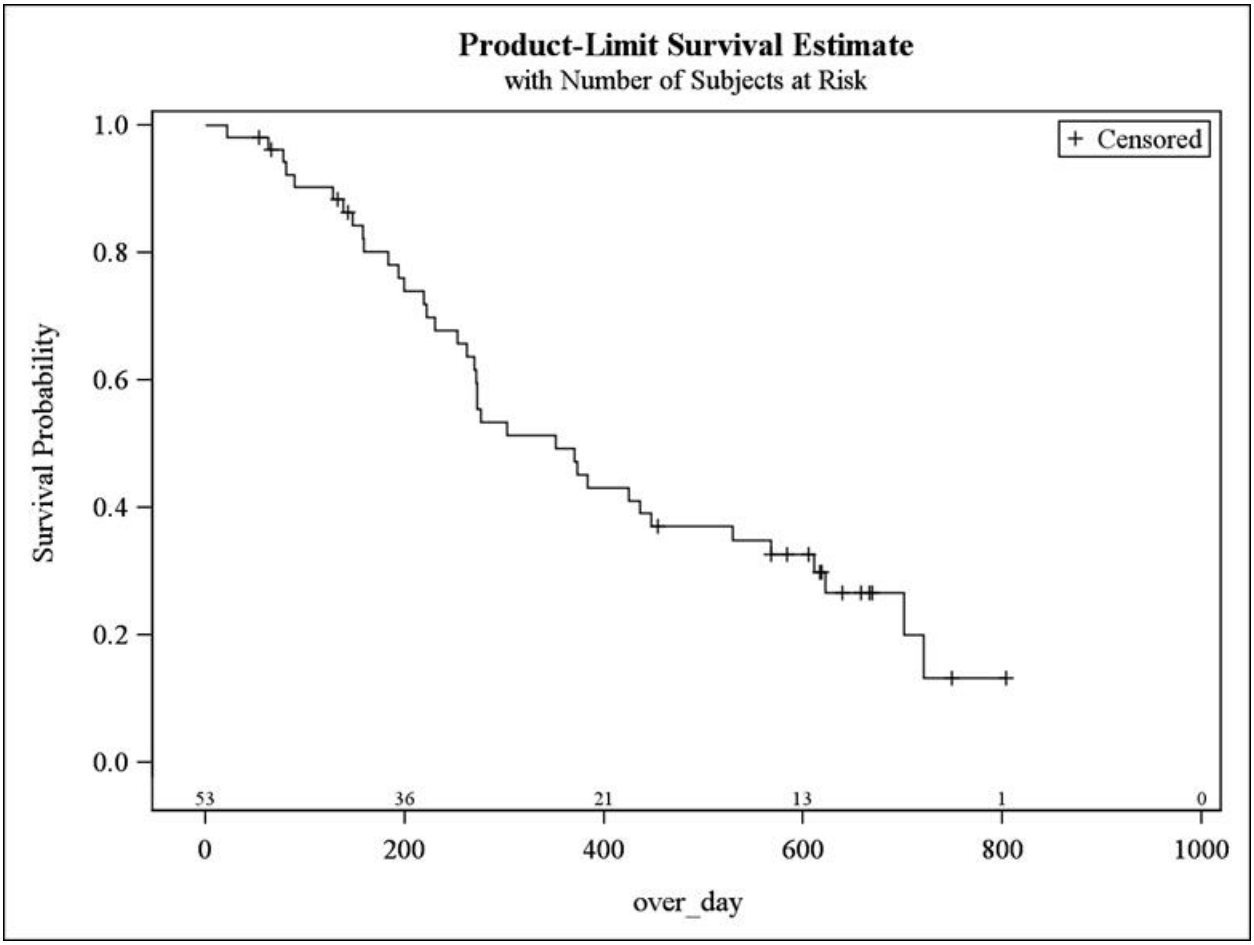
[a] Based on IWG 2006 MDS criteria; HI includes erythroid, platelet, or neutrophil response.

Source: Table MDS_RR_RESP01 (20 Nov 2015)

Overall survival (OS) was not significantly different (Log-Rank test P=0.7252) between the 60 and 90 mg/m^2 doses. Median OS for all r/r MDS subjects treated with guadecitabine was 352 days (11.7 months) (Figure 1). This was better than the median OS of 5.6 to 8.2 months (see Table 5) reported in several retrospective and prospective studies in patients who failed prior HMAs (Prebet et al 2011; Braun et al 2013; Garcia-Manero et al 2016).

DNA methylation data were available for 53 subjects with r/r MDS. Average maximum LINE-1 methylation relative to baseline was also similar for the 60 and 90 mg/m^2 dose groups.

Figure 1: Overall Survival: All (60 and 90 mg/m^2 Dose Groups Combined) Relapsed/Refractory MDS Subjects (Phase 2, Study SGI-110-01)



Source: MDS_RR_SURVIVAL02 (13 Nov 2015)

The incidence of common AEs Grade ≥3 was generally similar between the dose groups. A higher incidence of Grade ≥3 pneumonia, leukopenia, and sepsis was observed in the 90 mg/m^2 group (Table 3).

Table 3: Summary of Common (≥10% of Total) Adverse Events Grade ≥3 Regardless of Relationship to Guadecitabine: Relapsed/Refractory MDS Subjects (Phase 2, Study SGI-110-01)

	Number (%) of Subjects		
MedDRA Preferred Term	**60 mg/m^2 (N=26)**	**90 mg/m^2 (N=27)**	**Total (N=53)**
Any Grade ≥3 AE	22 (84.6%)	27 (100.0%)	49 (92.5%)
Thrombocytopenia	14 (53.8%)	15 (55.6%)	29 (54.7%)
Anemia	14 (53.8%)	13 (48.1%)	27 (50.9%)
Neutropenia	13 (50.0%)	11 (40.7%)	24 (45.3%)
Febrile neutropenia	10 (38.5%)	10 (37.0%)	20 (37.7%)
Pneumonia	6 (23.1%)	11 (40.7%)	17 (32.1%)
Fatigue	3 (11.5%)	4 (14.8%)	7 (13.2%)
Leukopenia	2 (7.7%)	4 (14.8%)	6 (11.3%)
Sepsis	2 (7.7%)	4 (14.8%)	6 (11.3%)

Source: MDS_RR_AE_G3 6.5 (13 Nov 2015)

Table 4 presents all-cause mortality in r/r MDS subjects. Of the 53 subjects with r/r MDS, 5 (9.4%) deaths occurred during the first 90 days of treatment, and 4 of the 5 patients were in the 90 mg/m^2 dose group. None of the subjects in the 60 mg/m^2 group died within the first 60 days of treatment.

Table 4: All-Cause Early Mortality: Relapsed/Refractory MDS Subjects (Phase 2, Study SGI-110-01)

		Number (%) of Subjects		
Dose	**N**	**30-day Mortality**	**60-day Mortality**	**90-day Mortality**
60 mg/m^2	26	0	0	1 (3.8%)
90 mg/m^2	27	1 (3.7%)	1 (3.7%)	4 (14.8%)
Total	53	1 (1.9%)	1 (1.9%)	5 (9.4%)

Source: Early Death for MDS RR (20 Nov 2015)

Based on the overall benefit-risk of the two dose groups (overall survival was not significantly different between the two dose groups with slight increase in certain Grade ≥3 AEs and early mortality at the 90 mg/m^2 dose group), we concluded that guadecitabine at the previously identified BED of 60 mg/m^2/day on Days 1-5 (Issa et al 2015) provides better overall benefit-risk profile and is the recommended dose for Phase 3.

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

(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

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 MDS/CMML. For more detailed information, please refer to the IB for guadecitabine.

Potential benefits of guadecitabine include symptom improvement, improvement in blood counts, decreased need for transfusions, delayed disease progression including progression to AML, 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, [redacted] pharmacodynamics (PD), and clinical data.

Guadecitabine's dinucleotide structure protects the active decitabine metabolite from inactivation by cytidine deaminase (CDA). Human[redacted] 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, 53 subjects with r/r MDS received guadecitabine. The observed overall response rate (CR+mCR+HI) was 43.4% and OS was 11.7 months, which exceeded that observed for currently available therapies in randomized, multicenter studies (Table 5).

Table 5: Guadecitabine Response and Survival Compared with Other Therapies for Subjects with Relapsed/Refractory MDS

	Number (%) Subjects				
	Phase 2 (SGI-110-01)	Prebet et al 2011[b]	Braun et al 2013	Garcia-Manero et al 2016	
Response	Guadecitabine (N=53)	Various Therapies after AZA failure (N=435)	DAC after AZA Failure (N=36)	Rigosertib (N=199)	BSC (N=100)
CR+mCR+HI, n (%)	23 (43.4%) [29~58][a]	NR	19%	NR	NR
Median OS (months)	11.7	5.6	7.3	8.2	5.9

AZA = azacitidine, DAC = Dacogen (decitabine), OS = overall survival, NR = not reported

[a] 95% CI based on a binomial distribution.

[b] Evaluated outcome of 435 patients with high-risk MDS after azacitidine failure using data collected from 4 independent data sets.

Source: Phase 2 SGI-110-01: Tables MDS_RR_RESP01 (20 Nov 2015) and MDS_RR_SURVIVAL02 (13 Nov 2015)

2.2 Rationale for Guadecitabine Dose and Regimen

As described previously, the BED determined in Phase 1 Dose Escalation was 60 mg/m^2. In Phase 2 Dose Expansion, 90 mg/m^2 was also investigated. Subjects with r/r MDS in Phase 2 Dose Expansion were randomized to receive 60 or 90 mg/m^2 guadecitabine SC Daily×5 in 28-day cycles. Overall survival (OS) was not significantly different (Log-Rank test P=0.7252) between the 60 and 90 mg/m^2 doses. Additionally, average maximum LINE-1 methylation relative to baseline was also similar for the 60 and 90 mg/m^2 dose groups using the Daily×5 dosing regimen (Issa et al 2015; Garcia-Manero et al 2014; Kantarjian et al 2013).

A higher incidence of Grade ≥3 pneumonia, leukopenia, and sepsis was observed in the 90 mg/m^2 group. All-cause mortality was also higher in subjects treated with the 90 vs 60 mg/m^2 (90-day: 14.8% vs 3.8%).

Based on the overall benefit-risk of the two dose groups (overall survival was not significantly different between the two dose groups with slight increase in certain Grade ≥3 AEs and early mortality at the 90 mg/m^2 dose group), it is concluded that guadecitabine at the previously identified BED of 60 mg/m^2/day provides better overall benefit-risk profile and is the recommended dose for Phase 3.

[redacted]

3.0 STUDY OBJECTIVES

3.1 Primary Objective

To assess and compare overall survival (OS) between guadecitabine and treatment choice (TC) in adults with MDS or CMML previously treated with a hypomethylating agent (azacitidine or decitabine, or both).

3.2 Secondary Objective(s)

To assess and compare effects of guadecitabine and TC in adults with MDS or CMML previously treated with a hypomethylating agent (azacitidine or decitabine, or both) with respect to the following variables:

- Transfusion independence.
- Marrow CR (mCR) with transfusion independence.
- Survival rate at 1 year after randomization.
- Leukemia-free survival.
- Number of days alive and out of the hospital (NDAOH).
- Disease response based on IWG 2006 MDS criteria including CR, partial response (PR), mCR, and hematological improvement (HI; erythroid, platelet, or neutrophil response); and duration of response.
- Number of red blood cell (RBC) and platelet transfusions.
- 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 designed to evaluate the efficacy and safety of guadecitabine in subjects with MDS or CMML who failed or relapsed after adequate prior treatment with azacitidine, decitabine, or both. This global study will be conducted in approximately 15 countries. The study consists of a 21-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 408 subjects from approximately 100 study centers will be randomly assigned in a 2:1 ratio to either guadecitabine (approximately 272 subjects) or TC (approximately 136 subjects). Before randomization the investigator will assign each subject to one of the following TC options:

- Low-dose cytarabine (LDAC).
- Standard Intensive Chemotherapy (IC) of a 7+3 regimen.
- Best Supportive Care (BSC) only.

Best Supportive Care will be provided to all subjects as per standard and institutional practice. Randomization will be stratified by disease category (MDS vs CMML), BM blasts (BM blasts >10% vs BM blasts ≤10%), TC option (LDAC vs IC vs BSC), and study center region (North America vs the rest of the world [ROW]).

The TC comparator arm options and doses are described in greater detail in Section 7.2. Guadecitabine will be given SC at a dose of 60 mg/m^2 given daily on Days 1-5 in 28-day cycles (delayed as needed to allow blood count recovery). 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.

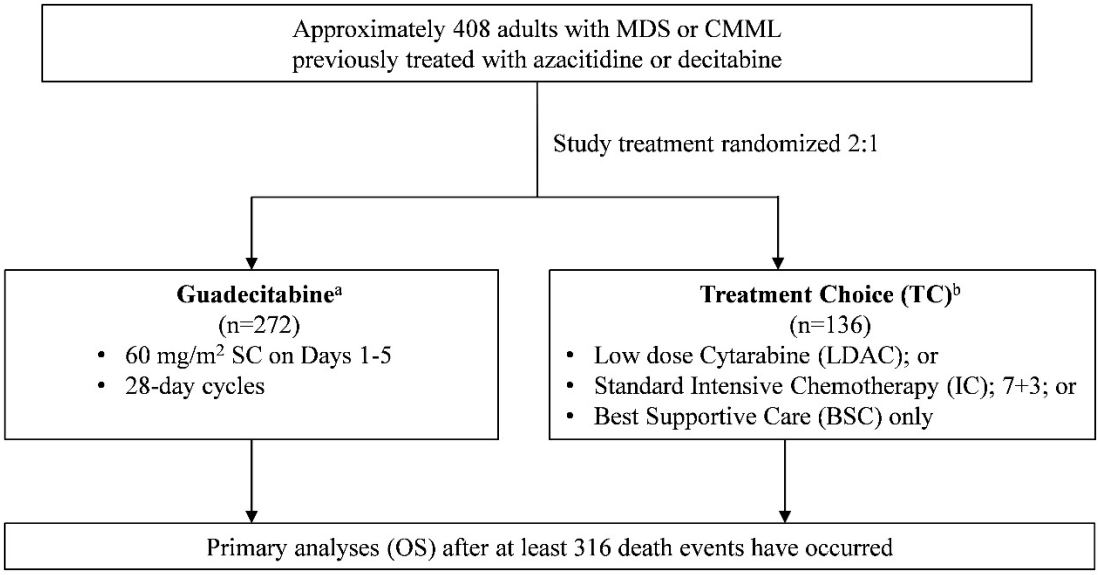
Subjects randomized to TC will not be allowed to cross over to guadecitabine. Both treatment groups also include BSC options, and hydroxyurea is allowed for subjects randomized to the TC arm only. BSC should be given according to standard and institutional practice.

Data will be reviewed by an independent Data Monitoring Committee (DMC) at regular intervals, primarily to evaluate safety during study conduct.

The primary efficacy endpoint is overall survival (OS), which will be assessed after at least 316 death events have occurred or as otherwise noted. 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 assessments 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 2: Study Schema



[a] Treatment with guadecitabine should continue 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.

[b] Before randomization the Investigator will assign each subject to one of the TC options.

4.2 Discussion of Study Design

This trial compares the efficacy and safety of guadecitabine to that of the treatment choices in patients with MDS or CMML who failed or relapsed after prior HMA treatment. Both azacitidine and decitabine are approved in many countries for treatment of MDS and CMML. Recent studies have shown that there may be cross-resistance between the 2 agents with little value of treating failed patients on one agent with the other one (Prebet et al 2011; Braun et al 2013). Therefore, this global trial mandates prior treatment with at least one of them, and patients who had prior treatment with both are also eligible.

Eligibility criteria proposed for this Phase 3 trial are similar to the eligibility criteria in the Phase 1-2 study (SGI-110-01 Dose Escalation and Dose Expansion). In this study, progression/relapse after prior adequate HMA treatment (at least 6 cycles unless progression prior to Cycle 6) is added together with clinical manifestations that require treatment, such as BM blasts >5% or transfusion dependence.

At present, there are no approved treatment options for patients with MDS or CMML who progress or relapse on HMA therapy or who fail to respond to at least 6 cycles of HMA treatment. For the comparator arm, the treatment choice options selected for this study are based on common "conventional care" regimens, which were used prior to HMA approvals in published trials (Fenaux et al 2009; Seymour et al 2010). Randomization ratio is 2:1 for guadecitabine and TC,

respectively to maximize the number of subjects on guadecitabine in the safety database for better safety assessment of the experimental agent.

Overall survival (OS) is the primary endpoint for this study and is a well-established and accepted standard endpoint to assess efficacy of a cancer treatment. The proposed secondary endpoints are additional measures of clinical benefit such as transfusion independence, complete response, days out of hospital, and quality of life. Safety will be assessed by incidence of adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) and by 30- and 60-day all-cause mortality.

This study is open-label. It is difficult to conduct such a trial in a blinded fashion because of the significant differences in the treatment schedules and the multiple treatment choices. The OS primary endpoint is not prone to observer bias.

4.3 Study Endpoints

4.3.1 Primary Endpoint

- OS, defined as the number of days from the day the subject was randomized to the date of death (regardless of cause).

4.3.2 Secondary Endpoints

- Transfusion independence for any 8 consecutive weeks based on rolling 8-week assessments. Number and rate of subjects who are free of transfusions for 8 consecutive weeks (or more) at any time after start of study treatment and who have Hgb of ≥8 g/dL and platelets $\geq 20 \times 10^9$/L.
- Marrow CR (mCR) based on IWG 2006 criteria with transfusion independence (as defined above).
- Survival rate at 1 year after randomization.
- Leukemia-free survival defined as the number of days from randomization to the date when BM or peripheral blood (PB) blasts reach ≥20%, or death of any cause.
- Number of days alive and out of the hospital (NDAOH).
- Disease response including CR, mCR, PR, and HI; including HI with erythroid (HI-E), neutrophil (HI-N), or platelet (HI-P) response, based on IWG 2006 criteria.
- Duration of response.
- Number of RBC or platelet transfusions (units) over the duration of the study treatment.
- Health-related QOL by EQ-5D™ (consisting of the EQ-5D-5L descriptive system and the EQ Visual Analogue Scale [EQ VAS]).
- Incidence and severity of AEs.
- 30- and 60-day all-cause mortality.

4.4 Data Monitoring Committee

A DMC will be established for this study. The DMC is an independent multidisciplinary group consisting of hematologic oncology experts and 1 biostatistician who, collectively, have experience in the treatment of subjects with MDS 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 408 subjects will be enrolled in this study at approximately 100 study centers in approximately 15 countries.

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 and comply with study procedures, and provide written informed consent before any study-specific procedure.
2) Cytologically or histologically confirmed diagnosis of MDS or CMML according to the 2008 World Health Organization (WHO) classification.
3) Performance status (ECOG) of 0-2.
4) Subjects with previously treated MDS or CMML, defined as prior treatment with at least one HMA (azacitidine and/or decitabine) for intermediate or high risk MDS or CMML whose disease progressed, relapsed, or was refractory to HMA treatment, as follows:
    a) Subject received HMA for at least 6 cycles and is transfusion dependent (as defined in 5b below), OR

b) Subject received HMA for at least 2 complete cycles and had disease progression defined as

i) ≥50% increase in bone marrow blasts from pre-HMA-treatment levels or from nadir post-HMA-treatment levels to >5% (for subjects with pretreatment or nadir blasts ≤5%) or to >10% (for subjects with pretreatment or nadir blasts >5%), and/or

ii) Transfusion dependent and ≥2g/dL reduction of Hgb from pre-HMA-treatment levels.

In addition to HMAs, other prior treatments for MDS such as lenalidomide, cytarabine, intensive chemotherapy, hydroxyurea, erythropoietin and other growth factors, or hematopoietic cell transplant (HCT) are allowed.

5) Subjects must have either:

a) Bone marrow blasts >5% at randomization, OR

b) Transfusion dependence, defined as having had transfusion (in the setting of active disease) of 2 or more units of RBC or platelets within 8 weeks prior to randomization.

6) Creatinine clearance or glomerular filtration rate ≥30 mL/min 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 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 and for at least 3 months after completing treatment and (b) while receiving treatment with LDAC or IC and for at least 6 months after completing treatment or for the duration specified in local prescribing information, whichever is longer. 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.

5.3 Exclusion Criteria

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

1) Subjects who have been diagnosed as having AML with peripheral blood or bone marrow blasts of ≥20%.

2) Subjects who may still be sensitive to repeated treatment with decitabine or azacitidine such as subjects who had response to prior decitabine or azacitidine treatment, but relapsed >6 months after stopping treatment with these agents.
3) Prior treatment with guadecitabine.
4) Hypersensitivity to decitabine, guadecitabine, or any of their excipients.
5) Second malignancy currently requiring active therapy, except breast or prostate cancer stable on or responding to endocrine therapy.
6) Treated with any investigational drug within 2 weeks of the first dose of study treatment.
7) Total serum bilirubin >2.5×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.
8) 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.
9) 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.
10) Refractory congestive heart failure unresponsive to medical treatment, active infection resistant to all antibiotics, or advanced non-MDS associated pulmonary disease requiring >2 liters per minute (LPM) oxygen.
11) Life expectancy of less than one month.
12) Subjects with TP53 mutation.

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, documented pregnancy, 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 electronic case report form (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 (see Section 10.4).

5.4.2 Withdrawal from the Study

Subjects may withdraw consent for the study at any time. 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 Data Monitoring Committee 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/MDS treatment, survival information, and safety data.

The investigator must also ensure the subject understands that his or her medical records will 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 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 study 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 2:1 between guadecitabine and TC groups, and will be stratified by disease category (MDS vs CMML), BM blasts (BM blasts >10% vs BM blasts ≤10%), TC option (LDAC vs IC vs BSC), 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.

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), which will be based on regional approvals per country and institutional standard practice.

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) will be supplied in a two-vial configuration.

SGI-110 for Injection, 100 mg [redacted]

SGI-110 Diluent for Reconstitution, 3 mL or 1.2 mL, [redacted]

Store the SGI-110 for Injection, 100 mg [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.

7.1.2 Guadecitabine Regimen and Administration

The guadecitabine regimen for this study is 60 mg/m^2 given SC daily on Days 1-5 in 28-day cycles (delayed as needed to allow blood count recovery, see Section 7.3.1). 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. Guadecitabine treatment benefit may not manifest until at least 2 to 3 cycles and full response may need 6 or more cycles so caution should be taken to avoid prematurely discontinuing treatment early after 1 to 2 cycles (Kropf et al 2015). Also maintaining treatment after response is essential to avoid quick relapse (Cabrero et al 2015). BSC should be given according to standard and institutional practice.

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 8.0).

Additional guidelines regarding SC injection will be detailed in the SGI-110-07 Pharmacy 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 Treatment Choice Active Comparator

The treatment choice options selected for this study include LDAC, standard IC (7+3 regimen), or BSC. The dosage regimens for the TC are as follows:

Low dose cytarabine (LDAC): given as 20 mg/m^2 SC or IV once daily for 14 days in 28-day cycles (delayed as needed to allow blood count recovery). Other schedules (eg, BID dosing) are

allowed if within institutional and standard practices. Treatment should be given for at least 4 cycles in the absence of disease progression or unacceptable toxicity. Subjects who are responding or have stable disease should continue treatment as per standard and institutional practice. BSC should be given as per institutional and standard practice.

Standard Intensive Chemotherapy (IC) of a 7+3 regimen: the recommended regimen of 7+3 is given as cytarabine 100-200 mg/m^2/day continuous infusion for 7 days and an anthracycline for 3 days. Anthracyclines are given according to local institutional practice and include but are not limited to: daunorubicin (45-60 mg/m^2/day), or idarubicin (9-12 mg/m^2/day), or mitoxantrone (8-12 mg/m^2/day) by intravenous infusion for 3 days. Subjects who achieve complete or partial response after IC induction should receive at least one or more additional cycles with reduced cytotoxic doses followed by BSC as per standard and institutional practice.

Best Supportive Care (BSC) only: given according to standard and institutional practice. BSC includes, but is not limited to 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.

BSC should also be given to all subjects in the study in all arms. Hydroxyurea is allowed for all subjects randomized to the TC arm, but is not allowed for guadecitabine arm. Hydroxyurea should be documented as a concomitant medication if the subject continues to receive their assigned TC option. If the subject permanently discontinued their assigned TC option, hydroxyurea treatment should be documented as subsequent anti-leukemia/MDS therapy.

If a subject must discontinue pre-assigned TC study treatment, alternative therapy 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.

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. To achieve initial dose intensity it is recommended to give the first 2 cycles at the recommended dose and schedule (60 mg/m^2 Daily×5 every 28 days). After the second cycle, subsequent guadecitabine dosing cycles should be guided by both pretreatment blood counts and the recovery of blood counts (blood counts just prior to or on Day 1 of the intended cycle) to pretreatment (previous cycle) ranges or better on Day 28. Since blood count suppression could also be due to the disease itself, pretreatment levels should be the guide to whether the subject needs dose delay or dose reduction or both according to the following table. However, if the investigator believes that the blood count suppression is due to disease and not drug, then treatment should be given on time at full dose. The trend of blood counts in the intermediate days (Days 8, 15, and 22) could be indicative of a

drug effect in case of lower counts than pretreatment levels by Day 8 and 15 with recovery trends by Day 22 or 29.

Table 6: Guidelines for Adjusting Guadecitabine Dosing after Cycle 2

Pretreatment Ranges	Day 29 of Treatment	Recommended Dosing
Neutrophils $\geq 1\times10^9$/L $<1\times10^9$/L to $\geq 0.5\times10^9$/L $<0.5\times10^9$/L	Recovered to the same range. In subjects with $<0.5\times10^9$/L, recovery should be at least to a similar number or higher as judged by the investigator.	60 mg/m^2/d as scheduled on Day 29.
	Did not recover to the same range as described above.	Wait for recovery up to 2 weeks. If counts recover within 1 week, give full dose. Otherwise, give 45 mg/m^2/d as soon as counts recover, but no later than Day 42. If further reduction is needed in subsequent cycles, reduce to 30 mg/m^2/d, then to 15 mg/m^2/d.
Platelets $\geq 50\times10^9$/L $<50\times10^9$/L to $\geq 25\times10^9$/L $<25\times10^9$/L	Recovered to the same range. In subjects with $<25\times10^9$/L recovery, should be at least to a similar number or higher as judged by the investigator.	60 mg/m^2/d as scheduled on Day 29.
	Did not recover to the same range as described above.	Wait for recovery up to 2 weeks. If counts recover within 1 week, give full dose. Otherwise, give 45 mg/m^2/d as soon as counts recover, but no later than Day 42. If further reduction is needed in subsequent cycles, reduce to 30 mg/m^2/d, then to 15 mg/m^2/d.

Following one or more cycles at a reduced dose, if the investigator believes that the subject is losing the beneficial response and can now tolerate a higher dose level, the subsequent cycle dose can be increased one level at a time to a maximum of 60 mg/m^2/d Daily×5 at the investigators discretion.

Investigators should always attempt to give guadecitabine for the full consecutive 5 days. If the consecutive 5-day treatment is interrupted (eg, due to the treatment day falling on a holiday or weekend, or other unforeseen circumstances), it should be resumed as quickly as possible so that the subject still receives the full 5-day course of treatment. For example, 3 days treatment, 1 to 2 days off if unavoidable, then 2 days treatment. In the rare cases of proliferative disease such as CMML, where counts are still high or increasing after treatment, earlier administration of guadecitabine before 28 days is allowed. In such subjects, hydroxyurea is also allowed for the first 30 days of guadecitabine treatment.

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 Prior and Concomitant Treatment

On the concomitant medication eCRF, document all medications a subject takes, starting from 21 days before randomization and ending 30 days after the last dose of study treatment. Prior anti-leukemia/MDS therapy should be documented regardless of timing with randomization. Include supportive or palliative treatment (see Section 7.4.1) whether prescription or nonprescription, and medications taken for procedures (eg, biopsy). Include start and stop dates and indication. Preventive measures may be prescribed according to institutional and standard practice. Hydroxyurea should be documented as a concomitant medication if the subject continues to receive their assigned TC option. If the subject permanently discontinued their assigned TC option, then hydroxyurea treatment should be documented as subsequent anti-leukemia/MDS therapy.

7.4.1 Supportive, Prophylactic, or Other Treatments

The investigator is permitted to prescribe all best supportive treatment(s) measures at his or her discretion and according to the best institutional and standard practice. All treatment options (guadecitabine and TC) may include BSC options. Appropriate hydration and supportive care, including blood and platelet transfusions, may be administered according to study-center standards. Aggressive surveillance, prophylaxis, and/or treatment of bacterial, fungal, viral, and opportunistic infections are essential to prevent morbidity and mortality.

Antibiotics and/or antifungals may be used to manage febrile neutropenia based on institutional standard practice.

Hematopoietic growth factors including ESAs such as erythropoietin are permitted. Iron chelating therapy is allowed as deemed necessary by institutional and standard practice.

All BSC measures including transfusions must be fully documented in the subjects' eCRFs.

Hydroxyurea is allowed for all subjects randomized to the TC arm, and is only allowed for subjects in the guadecitabine arm in the first 30 days of treatment. In the rare cases of proliferative disease such as CMML where counts are still high or increasing after treatment, earlier administration of guadecitabine before 28 days is also allowed.

Endocrine therapy is allowed for subjects with breast or prostate cancer who are stable on or responding to therapy.

All subsequent anti-leukemia/MDS therapy after discontinuation of study treatment must be documented in the eCRF.

7.4.2 Prohibited Medications

Other anticancer therapies, unless specified in the protocol (eg, endocrine therapy described above), 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 eCRF. Record any adverse clinical signs and symptoms associated with a potential overdose on the AE eCRFs. Report signs and symptoms of a potential overdose that meet serious adverse event (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

Dose limiting toxicities 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).

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. 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 infections events are also manifestations of the underlying disease of MDS and CMML, 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.

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 have been reported as related to guadecitabine, particularly at high doses when the drug may exert cytotoxic effects.

Refer to Section 7.3 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 and survival rate), transfusion (RBC and platelets) needs (independence and number of transfusions), response (CR, PR, mCR, and HI), 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. Transfusion requirements will be recorded every month in the first 6 months and then every 2 months thereafter. All hospital admissions will be documented and used to determine NDAOH.

Response Assessments: Clinical response will be determined based on blood sampling (peripheral blood [PB]) and BM aspirate or biopsy. If aspirate is not available and only bone marrow biopsy slides are provided, slides should include touch prep slides.

Response will be determined on Day 1 of each cycle based on PB at Day 1, and in cycles when BM aspirate or biopsy is done at or before Day 1, response assessment will be based on both PB and BM assessments. Blood will be collected at screening and on Days 1, 8, 15, and 22 of Cycles 1 and 2 and on Days 1 and 15 for Cycles 3 to 6. BM aspirate or biopsy will be performed at screening and at the end of Cycles 2, 4, and 6 (ie, Day 1 of Cycles 3, 5, and 7 [±7-day window]). Subjects treated with standard IC (TC arm) may have an additional BM aspirate or biopsy after the first cycle of induction in addition or instead of the end of Cycle 2 BM assessment. In cycles where BM is not required, use Day 1 PB and most recent prior BM data for response assessment.

After Cycle 6, BM assessment (BM aspirate or biopsy) will be repeated every 4 months until PB or BM assessment shows disease progression or relapse.

Clinical response will be determined based on the criteria provided in Table 7, which is based on the modified 2006 response criteria for MDS subjects (Cheson et al 2006).

Table 7: MDS Response Criteria

Complete Response (CR):		
Peripheral: Normal peripheral counts with granulocyte count ≥1.0×10^9/L, platelets ≥100×10^9/L and Hgb ≥11 g/dL.		
Marrow: Normal bone marrow with marrow blasts ≤5%. Persistent dysplasia will be noted.		
Partial Response (PR):		
Peripheral: Normal peripheral counts with granulocyte count ≥1.0×10^9/L, platelet count ≥100×10^9/L, and Hgb ≥11 g/dL.		
Marrow: Bone marrow blasts >5%, but were reduced by 50% or more from pretreatment levels.		
Marrow Complete Response (mCR):		
Reduction of bone marrow blasts to ≤5% and decrease by 50% or more with or without normalization of peripheral counts.		
Hematological Improvement (HI): lasts at least 8 weeks		
Erythroid Response (HI-E):	Major Response:	Hemoglobin increase ≥1.5 g/dL or relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 week compared with the pretreatment transfusion number in the previous 8 weeks.
Platelet Response (HI-P):	Major Response:	Absolute increase of platelet count from ≤20 to >20×10^9/L and by at least 100%, or if more than 20×10^9/L at baseline, by an absolute increase of at least 30×10^9/L.
Neutrophil Response (HI-N):	Major Response:	Granulocyte increase ≥100%, and by an absolute increase ≥0.5×10^9/L.

Note: Based on 2006 IWG criteria (adapted from Cheson et al 2006).

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 5 level health questionnaire (EQ-5D-5L) and EQ visual analog scale (EQ VAS), which will be administered before treatment on Day 1 (up to 4 days prior) of each cycle for the first 6 cycles (or monthly until 6 months after first treatment for subjects who discontinue treatment before 6 cycles). The QOL assessment tools are presented in Appendix 2.

[redacted]

[redacted]

9.4 Safety Assessments

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

9.5 Study Procedures

9.5.1 Schedule of Events

Table 8 presents the complete schedule of events for the study, with details following in text. Additional information on the study procedures is provided in the SGI-110-07 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 8: r/r MDS Phase 3 Schedule of Events

Cycles (28 Days)		**1 and 2**												**≥3**												**Safety FU[a]**	**Long Term Follow-Up[b]**
Cycle Day		1 (+7)*	2	3	4	5	6-7	8* (±2)	9	10	11-14	15* (±3)	22* (±3)	1 (+7)	2	3	4	5	6-7	8	9	10	11-14	15* (±3)		
Study Treatment[c]																											
Guadecitabine SC Days 1-5		X	X	X	X	X								X	X	X	X	X									
TC: LDAC SC or IV Days 1-14		X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X				
TC: Standard IC (7+3) Days 1-7		X	X	X	X	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	X	X	X	X	X	X	X			
Procedures	**Screening[d]**																										
Informed consent	X																										
Medical history/demographics (MDS/CMML diagnosis date)	X																										
Eligibility assessments	X																										
Physical examination[e]	X	X[e]												X[e]												X	
Vital signs[f]	X	X	X	X	X	X	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X	X	X	X	X	X[f]	X[f]	X[f]	X[f]	X[f]			X	
ECOG performance status	X	X												X												X	
12-lead ECG (triplicate)[g]		X																								X	
Health-related QOL (EQ-5D)[h]		X												X												X	X[b]
Height	X																										
Weight and BSA calculation (use height from screening)[i]	X	X[i]												X													
AEs/concomitant medications[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Prior therapies for MDS/CMML	X																										
Randomization (before dosing)	X[d]																										

Table 8: r/r MDS Phase 3 Schedule of Events (Contd)

Cycles (28 Days)		1 and 2												≥3										Safety FU[a]	Long-term Follow-Up[b]
Cycle Day		1 (+7)*	2	3	4	5	6-7	8* (±2)	9	10	11-14	15* (±3)	22* (±3)	1 (+7)	2	3	4	5	6-7	8	9	10	11-14	15* (±3)		
Laboratory Assessments	**Screening[d]**																								
Hematology[k]	X	X[k]						X				X	X	X[k]										X	X	X[b]
Serum chemistry[l]	X	X[l]												X[l]										X	X	
Urinalysis	X																									
Serum or urine pregnancy test[m]	X	X												X											X	
[redacted]		X				X								X												
[redacted]	X																									
Gene mutation (whole blood)[p]	X																									
Gene expression/methylation (blood)[q]	X													X											X	
Disease Assessments																										
BM aspirate or biopsy[r]	X													X												X[b]
Hospitalizations/Transfusions[s]	X	X						X				X	X	X										X	X	X[b]
Subsequent anti-leukemic/MDS therapy																									X	X
Disease progression status[t]																									X	X[b]
Survival follow-up																										X

* Day 1 7-day window only applies to Cycle 2. The Day 15 visit is not required after Cycle 6. (For subjects receiving TC, starting with Cycle 1, visits on Days 8, 15, and 22 are not required; instead institutional standards should be followed.)

[a] **Safety follow-up visit:** Must occur 30 (+7) calendar days after the last dose of study treatment or before the subject starts other anti-leukemia treatment, whichever is first. If the subject cannot attend the clinic, the visit may be conducted by telephone to collect, at minimum, AE and survival information. Safety follow-up visit may occur at the same time of treatment discontinuation only if decision to permanently discontinue treatment is made at least 30 days after last dose.

[b] **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 2 months (±2 weeks) until death. Health-related QOL is done only at monthly visits. Disease response assessments including conversion to AML (hematology and/or BM aspirate/biopsy) are done only for subjects who discontinued treatment before documented disease progression or relapse; assessments should be discontinued if subjects start other anti-leukemia treatment. Transfusion and hospitalization information are collected at all LTFU visits (monthly and every 2 months). Both monthly and every 2-month visits may be conducted by telephone if needed.

[c] **Study treatment:** For details on all treatment regimens, see Section 7.0.

[d] **Screening (and Randomization):** Screening must occur within 21 days of randomization, except that BM aspirate/biopsy may be collected within 28 days before randomization, [redacted] 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 apart.

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

[f] **Vital signs:** Assess before dosing on every dosing day in the clinic, after subject has rested in the sitting position for at least 3 minutes. Vital signs include blood pressure (systolic/diastolic), respiration rate, heart rate, and body temperature. Subjects assigned to TC should have vital signs measured on Day 1 of every cycle.

[g] **12-Lead ECG (triplicate):** Conduct predose and 1-2 hours postdose only on Day 1 of Cycle 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. Subjects assigned to BSC should be assessed once (in triplicate) on Cycle 1 Day 1 and once at the safety follow-up visit.

[h] **Health-related QOL**: Administer EQ-5D (consisting of the EQ-5D-5L descriptive system and the EQ VAS) before treatment on Day 1 (up to 4 days prior) of each cycle for at least 6 months. For subjects who discontinue treatment before Cycle 6, administer EQ-5D monthly until 6 months after the start of study treatment.

[i] **Weight and BSA (body surface area) calculation:** Weigh subject on Day 1 of each cycle (does not need to be repeated if done within 4 days of Day 1). BSA recalculation is only required if weight changes ±10% or more from the last calculation.

[j] **AEs/concomitant medications:** Document all study-procedure-related AEs from the time of informed consent to 30 days after the last dose of study treatment (unless otherwise specified in Section 10.3). Document all medications taken within 21 days before randomization to 30 days after the last dose of study treatment. For subjects receiving TC, visits after Day 1 of each cycle are not required; instead institutional standards should be followed.

[k] **Hematology:** Include complete blood count with differentials (a manual count should be conducted if there is suspicion of PB blasts; refer to Table 9.). Day 1 hematology for all cycles does not need to be repeated if done within 4 days of Day 1. For subjects receiving TC, hematology must be assessed on Day 1 of each cycle, but institutional standards should be followed for subsequent assessments. For Cycles >6, hematology will be required only on 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 Lab Manual.

[l] **Serum chemistry:** Refer to Table 9. 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 Lab Manual.

[m] **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]

[p] **Gene mutation:** Gene mutations analysis will done on whole blood collected during screening. TP53 assessments may be performed any time before randomization and may be done locally by the institution standard method.

[q] **Gene expression/methylation:** Blood sample for gene expression/methylation analysis should be collected from all subjects at screening and before dosing on Day 1 of Cycles 3, 5, and 7 and at the at the safety follow-up visit.

[r] **BM aspirate or biopsy:** BM aspirate and/or biopsy differential count will be performed according to local standard practice. The investigator will confirm eligibility using local lab data prior to randomization. Bone marrow aspirate or biopsy results may be collected within 28 days before randomization. BM aspirate is preferred; however, a biopsy should be done if no spicules are observed in the aspirate to include touch prep slides. Marrow aspirate or biopsy differential may include the following:

- Total cells counted
- Blasts (for CMML, blasts and blast equivalents include myeloblasts, monoblasts, and promonocytes)
- Promyelocytes
- Myelocytes
- Metamyelocytes
- Segmented neutrophils
- Eosinophils
- Basophils
- Lymphocytes
- Plasma cells
- Monocytes
- Pronormoblasts
- Normoblasts
- M:E ratio
- Auer rods
- Megakaryocytes: increased, normal, decreased, absent
- Presence of dysplasia: dysE, dysG, dysM
- Cellularity: % cellularity: hypocellular, hypercellular, normocellular
- Other

Detailed instructions on collection, labeling and shipping are described in the Study Lab Manual. A BM sample adequate for analysis must be obtained. Repeat the BM sample if not interpretable.

Response assessment is done on Day 1 of Cycles ≥2 based on BM aspirate/biopsy and the Day 1 PB. Assess PB at screening and on Day 1 of each cycle. Perform BM aspirate/biopsy at screening and then at the end of Cycles 2, 4, and 6 (ie, Day 1 of Cycles 3, 5, and 7 [±7-day window]). Subjects treated with standard IC may have an additional BM aspirate or biopsy after the first cycle of induction in addition or instead of the end of Cycle 2 BM assessment. Response will be assessed at each cycle on Day1 based on PB. In cycles when BM aspirate/biopsy is done on or before Day1, response will be based on both PB and BM. Subjects who discontinue treatment before Cycle 6 Day 1 before documented disease progression must undergo response assessment until confirmation of disease progression or relapse; assessment should be discontinued if subjects start other anti-leukemia treatment. After Cycle 6, repeat BM aspirate/biopsy every 4 months until PB or BM assessment shows disease progression or relapse, or other anti-leukemia treatment is started.

[s] **Hospitalizations/Transfusions:** Document all blood and platelet transfusions (blood product transfused and units) within 56 days before randomization to study termination, every visit including all LTFU visits. (For subjects receiving TC, visits after Day 1 of each cycle are not required; instead institutional standards should be followed.) Document all hospital admission and discharge dates and main reason for hospitalization, from Cycle 1 Day 1 and during all LTFU visits to study termination, every visit including all LTFU visits.

[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 SGI-110-07 Study Procedures Manual.

Bone marrow aspirate/biopsy may be collected within 28 days before randomization. Within 21 days before randomization, perform the following study procedures and tests, unless otherwise noted.

- 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 and list prior treatments and responses to these treatments. Document concurrent medical signs and symptoms to establish baseline conditions. Prior treatments for MDS/CMML or other hematologic disorder should be recorded.
- Investigator's confirmation of eligibility. Perform all necessary procedures and evaluations to document that the subject meets each eligibility criterion.
- Complete physical exam including 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.
- ECOG performance status (Appendix 1).
- Height measurement (for BSA calculation).
- All study-procedure-related AEs from the time of informed consent.
- Record all medications taken within 21 days before randomization.
- Blood and urine sample collection for laboratory assessments (See Table 9).
- 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.
- [redacted]
- Adequate BM aspirate slide or biopsy to include touch prep slide for baseline disease assessment by local lab, collected within 28 days before randomization.
- Blood sample collection for gene mutation analysis.
- [redacted]
- Document all blood and platelet transfusions (blood product transfused and units) performed within 56 days before randomization to confirm transfusion-dependence.

- 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 9: 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 allowed (analysis based on institutional standards) • Pregnancy test (if applicable)	• Pregnancy test (if applicable)

9.5.3 Treatment Procedures for Cycles 1 and 2

The following text represents assessments and procedures for Cycles 1 and 2 unless otherwise specified [redacted] and ECG assessments are done only in Cycle 1). Refer to Table 8. After randomization, visits will occur on every treatment day. In addition, visits will occur on Days 8, 15, and 22 of the first 2 cycles of therapy and on Days 1 and 15 of Cycles 3 through 6. (For subjects receiving TC, visits after Day 1 of each cycle are not required; instead institutional standards should be followed.) In Cycles >6, only treatment day visits are required, 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.

9.5.3.1 Day 1 (Before Dosing), Cycles 1 and 2

- Complete physical examination (does not need to be repeated if was done ≤4 days before Day 1).
- Vital signs.

- ECOG performance status (Appendix 1).
- 12-lead ECG (triplicate), Cycle 1 only.
- Health-related QOL (can be completed up to 4 days before Day 1) (Appendix 2).
- Weight and BSA calculation (use height from screening; BSA recalculation if weight changes ±10% or more from the last calculation; does not need to be repeated if was done ≤4 days before Day 1).
- All study-procedure-related AEs and concomitant medications.
- Sample collection for laboratory assessments, including:
  - Hematology (see Table 9) (does not need to be repeated if done ≤4 days before Day 1).
  - Serum chemistry (see Table 9) (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).
- 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.

9.5.3.2 Day 1 (After Dosing), Cycles 1 and 2

- 12-lead ECG (triplicate) in Cycle 1 only, 1 to 2 hours postdose (not applicable to subjects assigned to BSC).
- [redacted]
  - [redacted]
- All treatment-emergent AEs and concomitant medications.

9.5.3.3 Dosing Days, Cycles 1 and 2

- Vital signs (before dosing; not applicable to subjects assigned to BSC).
- All AEs and concomitant medications.
- [redacted]

9.5.3.4 Days 8, 15, and 22, Cycles 1 and 2

In addition to vital signs, which will be measured and recorded on dosing days as specified above, the following procedures will be performed on Days 8 (±2), 15 (±3), and 22 (±3) of Cycles 1 and 2

for subjects receiving guadecitabine. For subjects receiving TC, these visits are not required; instead institutional standards should be followed.

- All AEs and concomitant medications.
- Hematology (see Table 9).
- 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.

9.5.4 Treatment Procedures for ≥Cycles 3

Table 8 shows assessments and procedures for Cycles ≥3.

9.5.4.1 Day 1 (Before Dosing), Cycles ≥3

Day 1 for Cycles ≥3 has a visit window of +7 days, unless otherwise specified below.

- Complete physical examination (does not need to be repeated if was done ≤4 days before Day 1).
- Vital signs.
- ECOG performance status (Appendix 1).
- Health-related QOL (can be completed up to 4 days before Day 1) (Appendix 2).
- Weight and BSA calculation (use height from screening; BSA recalculation if weight changes ±10% from the last calculation; does not need to be repeated if was done ≤4 days before Day 1).
- All AEs and concomitant medications.
- Sample collection for laboratory assessments, within 4 days of Day 1, including:
  - Hematology (see Table 9).
  - Serum chemistry (see Table 9).
  - Serum or urine pregnancy test: for women of child-bearing potential only.
- [redacted]
- BM aspirate/biopsy required at the end of Cycles 2, 4, and 6 (Day 1 of Cycles 3, 5, and 7 [±7 days]) unless the subject has confirmed disease progression or relapse, or the subject started other anti-leukemia treatment.
- Assess response based on BM aspirate/biopsy and Day 1 PB. In cycles where BM is not required use Day 1 PB and most recent prior BM data for response assessment.
- 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.

9.5.4.2 Dosing Days, Cycles ≥3

- Vital signs (before dosing; not applicable to subjects assigned to BSC).
- All AEs and concomitant medications.
- [redacted]

9.5.4.3 Day 15, Cycles 3 to 6

The following procedures will be performed on Day 15 (±3) for Cycles 3 to 6 for subjects receiving guadecitabine. For subjects receiving TC, these visits are not required; instead institutional standards should be followed.

- All AEs and concomitant medications.
- Hematology (see Table 9).
- 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.

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 other anti-leukemia treatment, whichever is 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 9)

- Serum chemistry (see Table 9)
- Serum or urine pregnancy test for women of child-bearing potential only.
- [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 the last visit.
- Subsequent anti-leukemia/MDS therapy (regimen and start date).
- Disease progression status: Subjects who discontinue study treatment before documented disease progression must undergo response assessments (PB or BM aspirate/biopsy) until confirmation of disease progression or relapse; assessments should be discontinued if subjects start other anti-leukemia treatment.

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, 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 taken or as soon as possible thereafter. After subjects permanently discontinue study treatment and complete the safety follow-up visit, they are allowed to participate in other studies while still participating in this study for long-term follow-up.

9.5.6 Long-Term Follow-up

Long-term follow-up starts after a subject discontinues study treatment.

For subjects who discontinue study treatment before Cycle 6, long-term follow-up visits will occur monthly (±7 days) until 6 months after the start of study treatment. Procedures at monthly long-term follow-up visits include:

- 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-leukemia/MDS therapy (regimen and start date).
- Conversion to AML
- Survival follow-up.

After monthly visits for at least 6 months after the start of study treatment, long-term follow-up visits will be every 2 months (±2 weeks) until death. For subjects who discontinue study treatment

after Cycle 6, long-term follow-up visits are required every 2 months (±2 weeks), until death. Procedures at these visits include:

- 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 confirmation of disease progression or relapse; assessments should be discontinued if subjects start other anti-leukemia treatment.
- 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-leukemia/MDS therapy (regimen and start date).
- Conversion to AML
- Survival follow-up.

Long-term follow-up visits may be conducted by telephone if needed. If visit is conducted by phone please ensure to capture at a minimum hospitalization information, transfusion, subsequent anti-leukemia/MDS therapies, and survival status. If a subject refuses one or more long-term follow-up visits, survival status (at least) should be pursued, and the subject should remain on study unless the subject withdraws consent (Section 5.4.2). Every attempt should be made to obtain survival information on all subjects to protect the integrity of the primary endpoint analysis.

9.6 Unscheduled Visits

Additional visits (not specified in Table 8) 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.

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-leukemia/MDS treatment, including new investigational treatment, whichever occurs earlier. 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 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 4.03, 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 dose of study treatment 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 dose of study treatment and 60 days after the last dose of study treatment. Any female subjects receiving study treatment 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	S110SAEPhase3@astx.com
Global Phone	+1 (925) 558-4796
North America Toll-Free Fax	+1 (877) 589-0546

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 (1) to resolution, (2) until the investigator assesses the subject as stable and the event is following a clinically expected outcome, or (3) until the subject is lost to follow-up 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 89% to detect a difference in hazard ratio of approximately 0.68 (median OS of 6 months for the TC control arm and 8.8 months for the guadecitabine arm) using a 2-sided stratified log-rank test at an overall 2-sided 0.05 alpha level, given the use of a 2:1 randomization, the trial will require 316 death events. Assuming accrual is uniform over an 18-month enrollment period with an additional follow-up of 9 months, approximately 408 subjects will need to be randomized. If, after a follow-up of 12 months from the last subject randomized, the 316 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. If at 12 months 277 deaths events have not been observed, the primary analysis will be conducted when 277 death events have been observed (corresponding to 85% power).

11.2 Analysis Sets

11.2.1 All Subject Analysis Set

This analysis set will include information of 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

The Efficacy Analysis Set will include data from all randomized subjects. All data will be included and no subjects excluded because of protocol violations. Subjects will be included in the treatment group according to their randomly assigned treatment.

11.2.3 Safety Data Set

This 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.

11.3 Schedule of Analyses

Data listings and summary tables will be reviewed by the DMC approximately every 6 months (refer to Section 4.4) to ensure the safety of study subjects and to enhance the quality of trial conduct.

One interim analysis of OS is planned after approximately half of the required death events have occurred. This interim analysis will be conducted by an independent DMC. Final analyses of all study data will be performed after at least 316 death events have occurred or as otherwise noted.

11.4 Disposition

The number and percentage (n, %) of subjects enrolled, treated, lost to follow-up, and withdrawn (with reason) will be summarized. Sample size for efficacy and safety analysis sets will be clearly identified for each treatment group. All screened subjects will be included in 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. Summaries will be provided separately for each treatment group and both groups combined. The Efficacy and Safety Analysis Sets will be used for the summaries.

11.6 Efficacy Analyses

Unless otherwise specified, the Efficacy Analysis Set will be used for all efficacy analyses. This section describes the analyses conducted at the primary analysis time point, unless otherwise noted, when at least 316 death events have occurred, assuming that the study continued after the planned interim 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 Analyses

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 compared between the 2 treatment groups (guadecitabine and TC) using a stratified log-rank test with an overall 2-sided alpha level of 0.05, accounting for the alpha already spent during the interim analysis as described in Section 11.10. The stratification factors include disease category (MDS vs CMML), baseline BM blasts (>10% vs ≤10%), TC option (LDAC vs IC vs BSC), and study center region (North America vs ROW). Median OS and quartiles estimates will be provided for each treatment group using Kaplan-Meier procedure along with 95% confidence intervals (CIs).

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

If statistical significance is achieved for the primary efficacy endpoint of OS (at the 2-sided overall alpha level of 0.05), then hierarchically the secondary endpoints of 8-week transfusion independence, mCR with transfusion independence, 1-year survival rate, leukemia-free survival, and NDAOH will be compared between the treatment groups as addressed in Section 11.6.3.

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 Transfusion Independence

Transfusion independence after treatment is defined as no transfusions (no RBCs and no platelets) for 8 consecutive weeks, while maintaining Hgb ≥8 g/dL and platelets $\geq 20 \times 10^9$/L. Transfusion independence rate will be calculated as the number of subjects who achieve transfusion independence divided by the number of subjects included in the Efficacy Analysis Set, and will be compared between the 2 treatment groups using a Cochran Mantel-Haenszel test stratified by randomization stratification factors. Mantel-Haenszel weighted difference of transfusion independence rates and the associated CI will be provided. Additional sensitivity analyses will describe transfusion independence rates at 16 and 24 weeks.

11.6.2.2 Marrow CR with Transfusion Independence

The proportion of subjects who have achieved mCR and transfusion independence simultaneously will be calculated for each group. Comparison of the proportions between the two treatment groups will be made using Cochran Mantel-Haenszel test stratified by the randomization stratification factors. Mantel-Haenszel weighted difference in the proportions between the 2 treatment groups, and the associated CI will be provided.

11.6.2.3 One Year Survival Rate

One year survival rate is defined as the survival rate at the end of the first year from randomization. One year survival rate for each treatment group will be estimated by Kaplan-Meier procedure. 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.

11.6.2.4 Leukemia-Free Survival

The earliest date when subjects have BM or PB blasts ≥20%, or death of any cause is the event date of leukemia-free survival. Comparison of leukemia-free survival will be made using log-rank test stratified by the same stratification factors as in the OS analysis. Subjects who do not have events in leukemia-free survival will be censored on the last date of BM or PB blasts assessment, whichever is later. Medians and quartiles of leukemia-free survival and their CIs will be estimated by Kaplan-Meier procedure for each treatment group.

11.6.2.5 Number of Days Alive and Out of Hospital

The date of each hospital admission and discharge will be collected for each subject. Only the number of days when subjects are still alive and out of hospital during the first 6 months of the study will be included in this analysis. The NDAOH 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.

11.6.2.6 Disease Responses

CR, mCR, PR, and HI (also HI-E, HI-P, and HI-N separately) will be summarized for each treatment group. The rate of each response status and their CIs will be provided by treatment group.

11.6.2.7 Duration of Response

Duration of response (in number of days) will be calculated from the first date the response is observed to the date when the response criteria are no longer met. Duration of response will be summarized using mean, standard deviation, minimum, median, and maximum for subjects who achieve a response during the study.

11.6.2.8 Number of Red Blood Cell or Platelet Transfusion

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. The average number of RBC and platelet transfusions per month (up to Day 180) will be summarized separately by treatment group.

11.6.2.9 Health-related QOL (EQ-5D-5L and EQ VAS)

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). Only the data collected in the first 6 months of the study will be included in this analysis. The EQ-5D-5L index value and VAS and their respective changes from baseline will be summarized by visit. 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.

11.6.3 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:

- 8-week transfusion independence.
- Marrow CR (mCR) with transfusion independence.
- Survival rate at 1 year after randomization.
- Leukemia-free survival.
- Number of days alive and out of the hospital.

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 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.

[redacted]

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 and serum chemistry), 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 Preferred Term (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 (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-cancer treatment for MDS/CMML and subsequent AML, 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 (Kratz 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.

[redacted]

11.10 Interim Analysis

One interim analysis of OS is planned with a maximum spendable alpha of 0.01. This interim analysis will be conducted by the independent DMC after approximately half (ie, approximately 158) of the required 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.

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 27 months including 18 months for completing enrollment and approximately 9 months (based on the anticipated number of death events) follow up before final analysis. The study is expected to start in Q4 2016 and end in Q1 2019.

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 documents (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.
- Substantial changes in risk-benefit considerations.
- IMP becomes unavailable.

14.1.1 Study Supplies

Refer to the SGI-110-07 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), 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 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 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 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 eCRF. Incomplete or inconsistent data on the 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 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 eCRFs for each subject are based. They are to be separate and distinct from eCRFs, except for cases in which the sponsor has predetermined that direct data entry into specified pages of the subject's 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 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.

[redacted]

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 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. 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 and accruals of eligible subjects and data in the study shall be listed as lead authors on manuscripts and reports of study results. The sponsor's medical monitor, study director and/or lead statistician may also be included in the list of authors. This custom can be adjusted upon mutual agreement of the authors and Astex Pharmaceuticals. In addition, other than clinical pharmacology studies in healthy volunteers or Phase 1 studies, all clinical studies must be registered with ClinicalTrials.gov.

16.0 REFERENCES

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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 20 May 2016)

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

The attached sample (in English) was downloaded from the EuroQol website:
http://www.euroqol.org/home.html
(accessed on 24 November 2014)

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

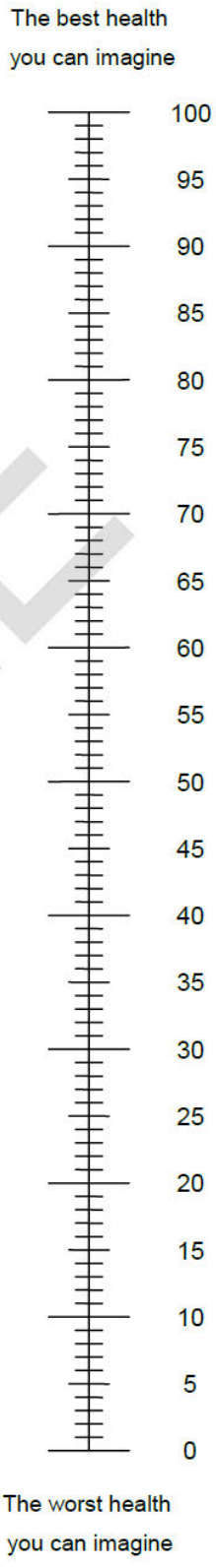
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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.

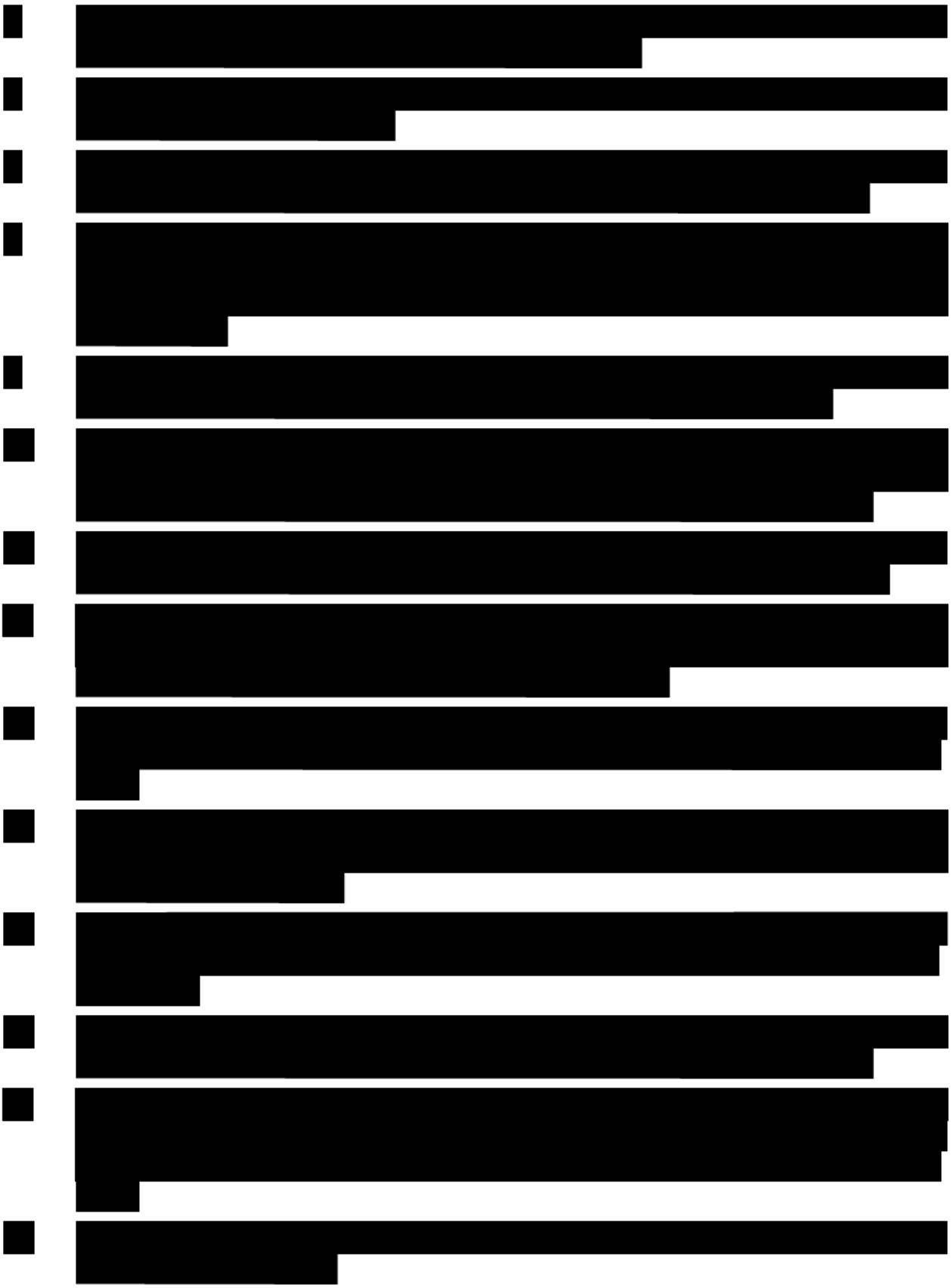
YOUR HEALTH TODAY = ☐



[redacted]

[redacted]

[redacted]



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