Official Title:	**An Open-label, Multicenter, Extension Study for Subjects who Participated in Prior Guadecitabine Clinical Studies**
NCT Number:	NCT03603964
Document Date:	Protocol Version Original: 19 January 2018

Clinical Study Protocol — SGI-110-12

An Open-Label, Multicenter, Extension Study for Subjects Who Participated in Prior Guadecitabine Clinical Studies

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PROTOCOL TITLE PAGE

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Study Clinical Phase:	Phase 2
Version Date:	Original (19 January 2018)

SPONSOR AND INVESTIGATOR SIGNATURE PAGE

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Study Acknowledgement

An Open-Label, Multicenter, Extension Study for Subjects Who Participated in Prior Guadecitabine Clinical Studies

Original (19 January 2018)

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

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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

An Open-Label, Multicenter, Extension Study for Subjects Who Participated in Prior Guadecitabine Clinical Studies

Original (19 January 2018)

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PROTOCOL APPROVAL PAGE

An Open-Label, Multicenter, Extension Study for Subjects Who Participated in Prior Guadecitabine Clinical Studies

Original (19 January 2018)

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PROTOCOL SYNOPSIS

Study Number and Title:
SGI-110-12: An Open-Label, Multicenter, Extension Study for Subjects Who Participated in Prior Guadecitabine Clinical Studies

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

Clinical Phase: 2

Study Centers Planned/Country: Multicenter global study (approximately 150 centers in approximately 20 countries)

Study Objective(s):

Primary Objective

- To provide ongoing treatment with guadecitabine for subjects who benefitted from guadecitabine treatment in a previous Astex-sponsored clinical study and to obtain long-term safety information.

Secondary Objective(s)

- To obtain long-term survival information on subjects who participated in a previous Astex-sponsored guadecitabine clinical study.

Study Design and Investigational Plan:

This is a multicenter, open-label extension study for subjects who participated in a previous Astex-sponsored guadecitabine clinical study (including but not limited to SGI-110-01, SGI-110-04, SGI-110-05, SGI-110-06, and SGI-110-07).

Subjects who were still receiving treatment with guadecitabine and in the opinion of the investigator were still benefitting from treatment at the time of database close of the original study will be eligible to participate in this extension study. Approximately 250 subjects could be enrolled.

Subjects will attend clinic visits on Days 1-5 of each 28-day cycle to receive treatment with guadecitabine. Data collection will be limited to treatment exposure, adverse events, concomitant medications, limited laboratory parameters, and survival status.

Study Population:

Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria:

1. Previous participation in an Astex-sponsored guadecitabine clinical trial (including but not limited to SGI-110-01, SGI-110-04, SGI-110-05, SGI-110-06, and SGI-110-07), in which the subject was treated with guadecitabine and was still on active treatment with guadecitabine at the time of database close for the prior study.
2. Subject is considered to be benefitting from guadecitabine treatment in the opinion of the treating investigator.
3. Subject is able to understand and comply with the study procedures, understand the risks involved in the study, and provide written informed consent before any study-specific procedure.
4. Women of childbearing potential (according to recommendations of the Clinical Trial Facilitation Group [CTFG]; see protocol Section 5.2 for details) 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 (as described in Section 5.2) and must agree not to become pregnant or father a child while receiving guadecitabine and for at least 3 months after completing guadecitabine treatment.

Exclusion Criteria

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

1. Any subject who, in the opinion of the investigator, may have other conditions, organ dysfunction, or have safety data from their prior study participation that suggest that the risks of continuing treatment with guadecitabine may outweigh the benefits.

Study Treatment:
Subjects will receive guadecitabine treatment at the same dose that they were receiving in the last cycle of their prior study or at a different dose as guided by the dose adjustment guidelines in the prior study protocol. Subsequent treatment delays and/or dose reduction are at the discretion of the investigator as guided by the dose adjustment guidelines of the prior study protocol. Treatment may continue as long as the subject continues to benefit based on investigator judgment.
There is no restriction on the use of best supportive care or hydroxyurea. Subjects who need to receive other anticancer therapies or other investigational treatments will be withdrawn from this study.

Study Endpoints:
Primary Endpoint
- Safety as measured by adverse events.

Secondary Endpoint
- Survival status.

Study Assessments and Procedures:
Informed consent and eligibility assessment (physical examination and hematology/laboratory assessments to judge continued favorable benefit/risk assessment) will be performed at screening.
Subjects will attend the clinic for treatment with guadecitabine on Days 1-5 of each 28-day cycle. When treatment is permanently discontinued, follow-up will stop with the safety follow-up visit occurring 30 ± 7 days after the last guadecitabine treatment or when an alternative anticancer treatment is administered, whichever occurs first.
Adverse events and concomitant medications will be collected throughout the study. Samples for limited hematology and serum chemistry assessments will be collected at screening, Day 1 of each cycle, and at the safety follow-up visit. For women of childbearing potential, a pregnancy test will be performed at screening and on Day 1 of each cycle prior to treatment. Survival status will be recorded when the subject is withdrawn from the study. Other clinical assessments may be performed as part of standard of care but the performance and results of these assessments will not be collected for this study.

Sample Size and Statistical Analyses:
There is no sample size requirement for this extension study. Summaries of treatment exposure and adverse events may be provided. The timing of such analyses will depend on the needs of the clinical development program.

Study Duration and Termination:
The study is expected to start in Q2 2018. The study may continue as long as subjects are receiving treatment with guadecitabine, or until guadecitabine becomes commercially available (anticipated for Q4 of 2019).

Compliance Statement:
The study will be conducted in accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, 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
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine transaminase (serum glutamic pyruvic transaminase [SGPT])
AML	acute myeloid leukemia
AST	aspartate transaminase (serum glutamic oxaloacetic transaminase [SGOT])
BSA	body surface area
CFR	Code of Federal Regulations
CMML	chronic myelomonocytic leukemia
CpG	cytosine-phosphate-guanine
CRF/eCRF	case report form/electronic case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
DNMT	DNA methyl transferase
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HCC	hepatocellular carcinoma
HMA	hypomethylating agent
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IMP	investigational medicinal product (the specific Astex drug product under study)
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LINE-1	long interspersed nuclear element-1
MDS	myeloid dysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MSDS	Material Safety Data Sheet
OHSA	Occupational Health and Safety
PK	pharmacokinetic(s)
PT	Preferred Term
RBC	red blood cell
r/r	relapsed/refractory
SAE	serious adverse event
SC	subcutaneous
SOC	System Organ Class
SUSAR	serious unexpected suspected adverse reaction
TC	treatment choice
TK	toxicokinetics
TN	treatment naïve
WBC	white blood cell

The study will be conducted in accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, 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

Guadecitabine (SGI-110) is a next-generation hypomethylating agent (HMA) being evaluated in subjects with hematological malignancies including acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), and chronic myelomonocytic leukemia (CMML), and solid tumors including ovarian cancer and hepatocellular carcinoma (HCC). This is an extension study to allow ongoing treatment with guadecitabine for subjects who have benefitted from treatment with guadecitabine in prior guadecitabine clinical studies. Descriptions of the different disease conditions under study and treatment options for each are provided in the respective prior study protocols.

1.1 Guadecitabine Mechanism of Action

Guadecitabine is a potent inhibitor of DNA methylation. Guadecitabine is a dinucleotide of decitabine and deoxyguanosine linked with a phosphodiester bond. Decitabine is the active metabolite. Guadecitabine is a new chemical entity that was designed to enhance pharmacokinetic properties compared with decitabine, with potential to improve pharmacodynamics, clinical efficacy, and safety. Unlike decitabine, guadecitabine is resistant to deamination by cytidine deaminases. Guadecitabine is cleaved by intra- and extracellular phosphorylases and other enzymes, releasing decitabine. This cleavage results in gradual release of decitabine both extra- and intracellularly, thus prolonging the exposure of tumor cells to its active metabolite decitabine compared to parental decitabine.

Guadecitabine (and decitabine) reverses DNA hypermethylation by inhibiting DNA methyl transferase (DNMT) enzymes. Hypermethylation of cytosine-phosphate-guanine (CpG) rich regions (CpG islands) is a physiologic mechanism of permanent gene inactivation that is usurped by leukemic cells, which use it to silence tumor suppressor genes and related proteins (Gore 2009). Decitabine is a cytidine analog that inhibits DNA methylation in vitro, resulting in re-expression of previously silenced genes (Steensma 2009). Decitabine appears to have a dual action on neoplastic cells. By incorporation into DNA and covalent bond formation with DNMT, decitabine effectively depletes the cells of methylating enzymes (Steensma 2009). This enzyme deficiency renders the cell unable to maintain DNA methylation after cellular replication, resulting in effective hypomethylation. However, the requirement for cell division to achieve hypomethylation and the short half-life of decitabine suggest that prolonged exposure is preferable for achieving a differentiation effect (Steensma 2009). At high concentrations, covalently trapped DNMT acts as a bulky DNA adduct and results in cytotoxicity rather than hypomethylation.

1.2 Nonclinical Data on Guadecitabine

Guadecitabine has been studied for its pharmacodynamic effects on global DNA methylation and on the re-expression of specific genes that are silenced in cancer cells due to an altered methylation status of their DNA sequence. Global DNA methylation is evaluated through the pyrosequencing of long interspersed nuclear element-1 (LINE-1) in DNA extracted from blood or tumor tissue. Guadecitabine has been evaluated in several different in vitro and in vivo models of various types of cancer and in safety pharmacology studies.

The pharmacokinetic profile and the absorption, distribution, metabolism and excretion (ADME) of guadecitabine are well characterized in nonclinical species as well as humans. The single- and repeat-dose nonclinical pharmacokinetics (PK) and toxicokinetic (TK) profiles of guadecitabine and its active metabolite decitabine have been examined in several studies in mice, rats, rabbits, and monkeys.

A comprehensive program of in vitro and in vivo nonclinical toxicology studies has been conducted with guadecitabine including Good Laboratory Practice (GLP)-compliant subcutaneous (SC) toxicity studies in rats, rabbits, and monkeys, and in vitro genetic toxicity tests.

Details on nonclinical studies conducted with guadecitabine are provided in the prior study protocol and in the Investigator's Brochure (IB).

1.3 Clinical Data and Human Pharmacokinetics

Guadecitabine is being evaluated in patients with hematological malignancies (AML, MDS, and CMML) 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; Issa et al 2015; Kantarjian et al 2017; Roboz et al 2018), as well as in patients with ovarian cancer and HCC (Studies SGI-110-02 and SGI-110-03).

The clinical development program for guadecitabine includes 8 clinical studies, as follows:

- SGI-110-01 – Phase 1/2 study of guadecitabine monotherapy in 401 subjects with AML/MDS/CMML. Included a Phase 1 dose escalation and a Phase 2 dose expansion.
- SGI-110-02 – Phase 2 study of guadecitabine in combination with carboplatin in 120 subjects with platinum-resistant ovarian cancer.
- SGI-110-03 – Phase 2 study of guadecitabine monotherapy in 50 subjects with hepatocellular carcinoma.
- 343-14-001 – Phase 1 dose escalation study of guadecitabine monotherapy in 14 AML subjects conducted in Japan.
- SGI-110-04 – Phase 3 study of guadecitabine vs treatment choice (TC) in approximately 800 subjects with treatment- naïve (TN) AML.

- SGI-110-05 – Phase 1 ADME study in approximately 6 subjects with AML, MDS, or solid tumors.
- SGI-110-06 – Phase 3 study of guadecitabine vs TC in approximately 400 adults with previously treated AML.
- SGI-110-07 – Phase 3 study of guadecitabine vs TC in approximately 400 adults with MDS or CMML previously treated with hypomethylating agents.

Additional guadecitabine studies may be initiated in the future. A summary of available results from clinical studies is provided in the prior study protocol and the most recent IB.

1.4 Potential Risks and Benefits to Human Subjects

In the setting of AML/MDS, it is difficult to separate the risks associated with guadecitabine from those of the disease, as pancytopenia is a hallmark of both. Reported serious adverse events (SAEs) associated with guadecitabine include myelosuppression-induced pancytopenia and its typical sequelae, such as infection progressing to sepsis or pneumonia, multiorgan dysfunction secondary to hypotension and hypoxia, mucosal inflammation, and bleeding. In rare cases, the subject may experience drug-related hypersensitivity, described as facial edema or cellulitis. Subjects with solid tumors also experienced adverse events related to myelosuppression. These and other risks of guadecitabine in humans are described further in Section 8.0. For more detailed information, please refer to the IB for guadecitabine.

Preliminary data indicate clinical activity of guadecitabine in AML and MDS, with the potential benefits of 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. Hence, benefits of response to treatment may outweigh incremental risks of guadecitabine therapy. For patients with solid tumors receiving guadecitabine as a single agent or in combination, there are data suggestive of clinical activity; however, the risk/benefit ratio in solid tumors does not support use of guadecitabine outside of a clinical trial.

Risk-benefit considerations favor performance of this trial. Enrollment in this study is limited to subjects who have been receiving guadecitabine in a prior clinical trial and are benefitting from guadecitabine treatment based on the Investigator's assessment.

2.0 RATIONALE

2.1 Rationale for the Study

While mortality is the most common outcome for patients with the conditions being treated in guadecitabine clinical studies, a small proportion of subjects survive to the end of the study and continue to receive treatment with guadecitabine at the time of database close. Of the 401 subjects treated in the first guadecitabine clinical study (SGI-110-01), 8 subjects continue to receive guadecitabine treatment, with a treatment duration (as of November 2017) of 2.8 to 5.6 years

(34-68 cycles). Phase 3 Study SGI-110-04 will close in 2018 and it is expected that there will be subjects still benefitting from guadecitabine treatment at the time that study closes. Rather than have each clinical study remain open to allow continued guadecitabine treatment, this extension study will provide one protocol under which subjects who have benefitted from guadecitabine treatment may continue to receive guadecitabine.

2.2 Rationale for Guadecitabine Dose and Regimen

The guadecitabine dose and regimen administered in clinical studies has been different for different indications. Subjects in this study will continue receiving the guadecitabine dose and regimen that they were receiving in the last cycle of their prior study. The rationale for the dose and regimen is provided in the prior study protocols from which subjects will be enrolled into this extension study protocol.

3.0 STUDY OBJECTIVES

3.1 Primary Objective

- To provide ongoing treatment with guadecitabine for subjects who benefitted from guadecitabine treatment in a previous Astex-sponsored clinical study and obtain long-term safety information.

3.2 Secondary Objective(s)

- To obtain long-term survival information on subjects who participated in a previous Astex-sponsored guadecitabine clinical study.

4.0 INVESTIGATIONAL PLAN

4.1 Overall Study Design

This is a multicenter, open-label extension study for subjects who participated in a previous Astex-sponsored guadecitabine clinical study (including but not limited to SGI-110-01, SGI-110-04, SGI-110-05, SGI-110-06, and SGI-110-07).

Subjects who were still receiving treatment with guadecitabine and in the opinion of the investigator were still benefitting from treatment at the time of database close of the original study will be eligible to participate in this extension study. Approximately 250 subjects could be enrolled at approximately 150 centers in approximately 20 countries worldwide.

Subjects will attend clinic visits on Days 1-5 of each 28-day cycle to receive treatment with guadecitabine. Subjects will receive the same guadecitabine dose and regimen that they were receiving in the last cycle of the prior study. Dose adjustment is permitted under the same guidelines provided in the prior study protocol. Data collection will be limited to treatment exposure, adverse events, concomitant medications, limited laboratory parameters, and survival

status. Other clinical assessments may be performed as part of standard of care but the performance and results of these assessments will not be collected for this study.

Treatment may continue as long as the subject continues to benefit based on investigator judgment. Subjects who need to receive other anticancer therapies or other investigational treatments will be discontinued from this study. Subjects who are withdrawn from treatment will have a safety follow-up visit at 30 ±7 days after the last guadecitabine dose or prior to beginning alternative anticancer therapy, whichever comes first, and then will be withdrawn from the study.

The primary endpoint is safety as measured by adverse events. Survival status is a secondary endpoint.

4.2 Discussion of Study Design

This study is designed to allow ongoing treatment with guadecitabine to subjects who have benefitted from guadecitabine treatment in prior Astex-sponsored studies. To minimize the burden on study centers and subjects, assessments have been limited to those required to assess long-term safety.

The sample size of approximately 250 subjects is an estimate. Most of the subjects enrolled in this study will have participated in 1 of 3 ongoing Phase 3 studies that are to enroll a total of approximately 1600 subjects (Studies SGI-110-04, SGI-110-06, and SGI-110-07). Based on the number of death events needed for the primary analysis for each of those studies, the number of guadecitabine subjects receiving treatment at the end of the studies could range from 180 (assuming no treatment difference and no withdrawals) to 326 (assuming all survivors were guadecitabine subjects and no withdrawals). As more guadecitabine clinical studies are conducted, the number of subjects enrolled in this extension study could increase.

4.3 Study Endpoints

4.3.1 Primary Endpoint

- Safety as measured by adverse events

4.3.2 Secondary Endpoint

- Survival status

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Number of Subjects and Centers

Approximately 250 subjects will be enrolled in this study at approximately 150 study centers.

5.2 Inclusion Criteria

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

1. Previous participation in an Astex-sponsored guadecitabine clinical trial (including but not limited to SGI-110-01, SGI-110-04, SGI-110-05, SGI-110-06, and SGI-110-07), in which the subject was treated with guadecitabine and was still on active treatment with guadecitabine at the time of database close for the prior study.
2. Subject is considered to be benefitting from guadecitabine treatment in the opinion of the treating investigator.
3. Able to understand and comply with the study procedures, understand the risks involved in the study, and provide written informed consent before any study-specific procedure.
4. Women of child-bearing potential (according to recommendations of the Clinical Trial Facilitation Group [CTFG]; see below* for details) must not be pregnant or breastfeeding and must have a negative pregnancy test at screening. Women of child-bearing potential and men with female partners of child-bearing potential must agree to practice 2 highly effective contraceptive measures while receiving treatment with guadecitabine and for at least 3 months after completing treatment and must agree not to become pregnant or father a child while receiving study treatment and for at least 3 months after completing guadecitabine treatment. Contraceptive measures which may be considered highly effective comprise combined hormonal contraception (oral, vaginal, or transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, sexual abstinence, and surgically successful vasectomy. Abstinence is acceptable only if it is consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of birth control.

5.3 Exclusion Criteria

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

1. Any subject who, in the opinion of the investigator, may have other conditions, organ dysfunction, or have safety data from their prior study participation that suggest that the risks of continuing treatment with guadecitabine may outweigh the benefits.

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* According to recommendations of the CTFG (CTFG 2014), a woman is considered of childbearing potential (ie, fertile) following menarche and until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A man is considered fertile after puberty unless permanent sterile by bilateral orchidectomy.

5.4 Treatment Discontinuation and Withdrawal of Subjects

5.4.1 Discontinuation from Study Treatment

Subjects who permanently discontinue study treatment will attend a safety follow-up visit at 30 ± 7 days after the last dose of guadecitabine or prior to the start of alternative anticancer therapy, whichever comes first. Reasons for treatment discontinuation could include the following:

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

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

5.4.2 Withdrawal from the Study

Subjects may withdraw consent for the study at any time, or subjects may be lost to follow-up. 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 safety evaluation, such as adverse events.

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 PROCEDURES

Subjects will be screened at each study center for assessment of eligibility for the study. This screening may start once the date of data cut-off for the prior study has been determined.

All screened subjects will be assigned a unique identifier that will include the study number from their prior study.

7.0 STUDY TREATMENTS

Guadecitabine is the Investigational Medicinal Product (IMP).

7.1 Investigational Medicinal Product (IMP): 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 (SGI-110) will be supplied in a two-vial configuration.

SGI-110 for Injection, 100 mg is a glass vial containing lyophilized guadecitabine drug powder for reconstitution and SC injection using the custom diluent supplied in a separate vial. Each vial is stoppered and sealed with a flip-off cap.

SGI-110 Diluent for Reconstitution, is a glass vial of custom diluent. Each vial is stoppered and sealed with a flip-off cap. The diluent comprises 3 commonly used excipients, propylene glycol, glycerin, and ethanol, which are generally recognized as safe.

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

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

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

Please refer to the SGI-110-12 Pharmacy Manual for further information on guadecitabine including storage conditions.

7.1.2 IMP Regimens and Administration

Subjects will receive guadecitabine treatment at the same dose that they were receiving in the last cycle of their prior study or at a different dose as guided by the dose adjustment guidelines in the prior study protocol. Subsequent treatment delays and/or dose reduction are at the discretion of the investigator as guided by the dose adjustment guidelines of the prior study protocol. Treatment may continue as long as the subject continues to benefit based on investigator judgment.

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

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

Additional guidelines regarding SC injection will be detailed in the SGI-110-12 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.

There is no restriction on the use of best supportive care or hydroxyurea. Subjects who need to receive other anticancer therapies or other investigational treatments will be withdrawn from this study.

7.2 Guidelines for Adjusting or Withholding Study Treatment

Treatment delays and/or dose reduction are at the discretion of the investigator as guided by the dose adjustment guidelines of the prior study protocol.

7.3 Concomitant Treatment

On the concomitant medication eCRF, document all medications a subject takes, starting from the first day of treatment in this study and ending 30 days after the last dose of study treatment or when the subject begins alternative anticancer therapy, whichever comes first. Include supportive or palliative treatment (see Section 7.3.1) 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.

7.3.1 Supportive, Prophylactic, or Other Treatments

There is no restriction on the use of best supportive care or hydroxyurea. Give supportive treatment according to the institutional standard practice or other established standard of care guidelines.

7.3.2 Prohibited Medications

Other anticancer therapies (except those specified in Section 7.3.1 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.

Subjects who need to receive other anticancer therapies or other investigational treatments will be withdrawn from this study.

7.4 Overdose Instructions

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

Section 10.3). Treat any AE (including SAE) based on standard care for the specific signs and symptoms.

8.0 RISKS/PRECAUTIONS

Refer to the Guadecitabine IB for the most current risks and precautions, as well as a complete list of AEs considered expected with guadecitabine 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 (as described in Dacogen package insert [US] and Dacogen summary of product characteristics [EU]) would also be considered expected for guadecitabine.

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) for the 5-day regimen at a dose of 125 mg/m^2 SC and included thrombocytopenia (Grade 4), neutropenia (Grade 4), and sepsis (Grade 5).

8.2 Myelosuppression (Neutropenia, Febrile Neutropenia, Thrombocytopenia, and Anemia) and its Consequences (Infections and/or Hemorrhage)

Myelosuppression and its consequences (pneumonia, sepsis, and other infections and/or hemorrhage from thrombocytopenia) are the primary toxicities 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 infection events are also manifestations of the underlying disease of AML, 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 in the prior study protocol.

8.3 Fertility

Decitabine, the active metabolite of guadecitabine, alters fertility and is mutagenic. Because of the possibility of infertility, men should have sought advice on cryopreservation of sperm, and women of childbearing potential should have sought consultation regarding oocyte cryopreservation before study treatment was started in the prior study. 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 and 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 (relapsed/refractory [r/r] AML, TN AML, TN MDS, r/r MDS, N=308 [Phase 2 Dose Expansion]) treated with guadecitabine (60-90 mg/m^2 5-day regimen or 60 mg/m^2 10-day regimen in AML only) included 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.

Common AEs, regardless of relationship to guadecitabine, observed in subjects with advanced HCC who failed prior treatment with sorafenib (Study SGI-110-03) who were treated with guadecitabine (45-60 mg/m^2 5-day) included neutropenia, injection site events, fatigue, thrombocytopenia, and leukopenia. The most common SAE in these subjects was febrile neutropenia.

Common AEs, regardless of relationship to guadecitabine, observed in subjects with platinum-resistant recurrent ovarian cancer (Study SGI-110-02) who were treated with guadecitabine in combination with carboplatin included neutropenia, nausea, fatigue, vomiting, injection site events, constipation, abdominal pain, diarrhea, leukopenia, anemia, thrombocytopenia, and hypomagnesaemia. The most common SAEs in subjects in these subjects were small intestinal obstruction, vomiting, abdominal pain, febrile neutropenia, neutropenia, and nausea. Three subjects had drug-related SAEs (sepsis, pleural effusion, and febrile neutropenia) with an outcome of death.

9.0 STUDY ASSESSMENTS AND PROCEDURES

9.1 Efficacy Assessments

There are no efficacy assessments in this study, except for survival status which will be documented at the time of withdrawal from the study.

9.2 Safety Assessments

Safety assessments will be based on AEs, concomitant medications, and limited clinical laboratory parameters (hematology and chemistry).

9.3 Study Procedures

9.3.1 Schedule of Events

Table 1 presents the complete schedule of events with details following in text.

Additional procedures may be performed as part of standard of care but the performance and outcome of these assessments will not be collected as part of this study.

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 Institutional Review Board / Independent Ethics Committee (IRB/IEC) according to policy.

Table 1: Schedule of Events

	Screening (Day -14 to Day -1)	Each 28-day Cycle Day 1	2	3	4	5	Treatment Discontinuation/ Safety Follow Up[a]
Procedures							
Informed consent	X						
Physical examination[b]	X						
Hematology[c]	X	X					X
Serum chemistry[d]	X	X					X
Serum or urine pregnancy test[e]	X	X					X
Investigator's confirmation of eligibility	X						
Weight	X	X					
Height	X						
BSA calculation[f]	X	X[f]					
Guadecitabine treatment		X	X	X	X	X	
Adverse events		X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X
Survival status							X

[a] To be performed 30±7 days after the last guadecitabine dose or prior to the subject receiving alternative anticancer therapy, whichever comes first. If the subject cannot attend the clinic, the visit may be conducted by telephone to collect, at minimum, AE information.

[b] Complete physical examination includes weight and examination of body systems according to institutional standards. A complete physical examination is required.

[c] Hematology parameters will be limited to those identified in Table 2. Day 1 hematology for Cycle 1 does not need to be repeated if screening is done within 1 week of Cycle 1 Day 1. Collection, analysis, and reporting information are described in the Study Lab Manual.

[d] Serum chemistry parameters will be limited to creatinine and liver function tests, as identified in Table 2. Day 1 serum chemistry for Cycle 1 does not need to be repeated if screening is done within 2 weeks of Cycle 1 Day 1. Collection, analysis, and reporting information are described in the Study Lab Manual.

[e] Women of child-bearing potential only. The screening test must be done within 7 days of Cycle 1 Day 1; test not required on Cycle 1 Day 1 if done at screening.

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

9.3.2 Screening Procedures

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

Within 14 days before treatment administration, perform the following study procedures and tests:

- Written informed consent. The informed consent form (ICF) must be signed and dated by the subjects before any study-specific samples are collected or study-specific procedures are initiated.

- Complete physical exam including height and weight, and examination of body systems according to institutional standards.
- Serum or urine pregnancy test: for women of child-bearing potential only. Must be done within 7 days of Cycle 1 Day 1. Results must be negative for the subject to be eligible for enrollment into the study.
- Sample collection for clinical laboratory tests (hematology and serum chemistry; Table 2). Collection, analysis, and reporting information are described in the Study Lab Manual.
- BSA calculation.
- Investigator's confirmation of eligibility and favorable benefit/risk assessment for the subject. Perform all necessary procedures and evaluations to document that the subject meets each eligibility criterion.

Table 2: Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis	Serology
- Complete blood count (CBC) - Hemoglobin - RBC counts - WBC counts - Platelets - Absolute neutrophil count - WBC differential	- Albumin - Alkaline phosphatase - ALT - AST - Creatinine - Total bilirubin - Direct bilirubin (only if total bilirubin is elevated)	- Pregnancy test (if applicable)	- Pregnancy test (if applicable)

9.3.3 Treatment Procedures

Visits will occur on every treatment day (Days 1-5 of each 28-day cycle). The following procedures will be performed:

- Sample collection for clinical laboratory tests (Day 1 only) (Table 2), including hematology, serum chemistry, and pregnancy test for women of child-bearing potential (collect samples prior to guadecitabine treatment). For Cycle 1, Day 1 hematology and serum chemistry does not need to be repeated if screening is done within 1 week of Cycle 1 Day 1. Pregnancy test does not need to be repeated on Cycle 1 Day 1 if done at screening. Collection, analysis, and reporting information are described in the Study Lab Manual.
- Weight (Day 1 only). If weight has changed ±10% from the last measurement, BSA should be recalculated.
- Guadecitabine administration (Days 1-5).
- Adverse events and concomitant medications.

9.3.4 Treatment Discontinuation and Safety Follow-up Visit

Each subject should be followed up, 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 10.4). Subjects who withdraw consent should still be encouraged to complete this visit. If the subject is unable to attend the clinic, the visit may be conducted by telephone to collect AEs and survival status. If the subject discontinued guadecitabine treatment to receive alternative therapy, this visit should be conducted prior to the start of alternative therapy. The following evaluations are to be performed:

- Sample collection for clinical laboratory tests (Table 2), including hematology, serum chemistry, and pregnancy test for women of child-bearing potential. Collection, analysis, and reporting information are described in the Study Lab Manual.
- Adverse events and concomitant medications.
- Survival status.

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 anticancer treatment, including new investigational treatment, whichever occurs earlier.

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

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

Death is an outcome of an SAE and usually not itself an SAE, unless it is death with no identifiable cause or event. In all other cases, record the cause of death as the SAE. Investigators will assess

the status of previously reported, and occurrence of new AEs and SAEs at all subject evaluation time points during the study.

10.2.1 Severity

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

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

10.2.2 Relationship to Study Treatment (Suspected Adverse Reactions)

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

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 Exposure 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 Exposure 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 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	
Telephone Numbers	
Local Number:	[redacted]
North America Toll Free	[redacted]
Fax Numbers	
Local Fax:	[redacted]
Toll Free Fax	[redacted]
Email	
Drug Safety Inbox	[redacted]
Other countries: Refer to the Astex Fax Cover Sheet for the Drug Safety Department. All safety fax numbers are listed there.	

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

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

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

10.4 Follow-up for Adverse Events

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

11.0 STATISTICS

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

Data summaries and listings will be generated using SAS version 9.4 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. The clinical study report will describe deviations from the statistical analysis plan, if any.

11.1 Sample Size

There is no sample size requirement for this extension study. It is expected that approximately 250 subjects could be enrolled. As more guadecitabine clinical studies are conducted, the number of subjects enrolled in this extension study could increase.

11.2 Analysis Sets

All subjects who received any treatment during this study will be included in the analysis for this study.

11.3 Schedule of Analyses

There is no predetermined schedule of analyses for this study. Analyses may be performed during the course of the study depending on the needs of the clinical development program. Analyses may also be performed after the last subject has discontinued treatment and been withdrawn from the study.

11.4 Disposition

If required, the number and percentage (n, %) of subjects screened, enrolled, treated, and withdrawn (with reason) will be summarized. All screened subjects will be included in the disposition analysis.

11.5 Analysis of Demographic and Baseline Data

Demographic and baseline characteristics are not collected as part of this study. If summaries of demographic and baseline characteristics are required for this study, the relevant information will be obtained from the database of the prior study. If required, 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, or as appropriate depending on the purpose of the analysis.

11.6 Efficacy Analyses

Survival status is the only efficacy outcome collected as part of this study. Survival duration for each subject starting from the time of first guadecitabine treatment in the prior study may be determined.

11.7 Safety Analyses

Safety will be assessed by subject reported and investigator observed AEs, concomitant medications, and clinical laboratory tests (hematology, serum chemistry). If required, safety variables will be tabulated and presented for all subjects who receive any amount of guadecitabine. All safety data collected during the study will be included in the study database. In addition, summaries of exposure to guadecitabine and reasons for discontinuation may be provided.

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.

Treatment-emergent AEs will be defined as those occurring or worsening after starting study treatment under this study protocol. Summaries may be provided for all treatment-emergent AEs and SAEs, and treatment-emergent AEs and SAEs considered related to study treatment, as follows:

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

Laboratory values reported by different local labs will be listed. Summaries of laboratory data may be provided if deemed necessary.

11.8 Interim Analysis

No interim analysis will be performed for this study. Data summaries may be provided during the course of the study to meet the needs of the clinical development program.

11.9 Procedures for Handling Missing, Unused, and Spurious Data

No imputation of values for missing data will be performed. 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 study is expected to start in Q2 2018. The study may continue as long as subjects are receiving treatment with guadecitabine, or until guadecitabine becomes commercially available (anticipated for Q4 of 2019 at the earliest).

13.0 STUDY COMPLIANCE AND ETHICAL CONSIDERATIONS

13.1 Compliance Statement

The study will be conducted in accordance with the ICH GCP guidelines, 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 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 source document (including the date), and the form must be signed, before the subject undergoes any study-specific procedures.

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

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

14.0 ADMINISTRATIVE PROCEDURES

14.1 Sponsor Responsibilities

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

- Request by Health Authority to terminate the study
- Unsatisfactory subject enrollment with regard to quality or quantity
- Significant or numerous deviations from study protocol requirements, such as failures to perform required evaluations on subjects, maintain adequate study records or inaccurate, incomplete or late data recording on a recurrent basis

- The incidence or severity of AEs in this or other studies indicating a potential health hazard caused by the study treatment

14.1.1 Study Supplies

The sponsor will supply sufficient quantities of the following materials to each clinical center:

- Guadecitabine as described in Section 7.0.
- IB for guadecitabine.
- Case report forms or data collection tools.

14.1.2 Investigator Training

As part of the prior study protocols, all study centers had a center-specific study initiation meeting to ensure the center staff understood the protocol, study requirements, and data capture processes. This protocol contains no new processes or information beyond those in the prior study. 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 the 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.

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.

14.1.4 Study Monitoring

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

- Assure compliance with the study protocol and appropriate regulations.
- Verify that (1) the informed consent process was conducted before initiation of any study-specific procedures (ie, performed solely for the purpose of determining eligibility for the study) and before provision of study treatment, and (2) this process is adequately documented.
- Verify that the protocol, protocol amendments, and safety information are submitted to the IRB/IECs and approved by the IRB/IECs in a timely manner.

- Review the CRF/eCRFs and source documents to ensure that reported study data are accurate, complete, and verifiable from source documents.
- Verify that study treatments are stored properly and under the proper conditions, that they are in sufficient supply, and that receipt, use, and return of guadecitabine at the study centers is 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 treated.

14.2.2 Guadecitabine 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, supplies will be autorefilled.

Keep guadecitabine 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 guadecitabine 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 guadecitabine supplies and associated documentation.

Maintain an accurate accounting of the guadecitabine. 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 guadecitabine and other study material is destroyed or returned to the sponsor on completion of the study. If the guadecitabine 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. Guadecitabine accountability records must be maintained and readily available for inspection by representatives of Astex Pharmaceuticals and are open to inspections by regulatory authorities at any time.

14.2.3 Reporting and Recording of Study Data

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

The investigator must assure subject anonymity and protection of identities from unauthorized parties. On CRF/eCRFs or other documents or subject records provided to Astex Pharmaceuticals, identify subjects by code (subject number) and not by names. The principal investigator should maintain documents not for submission to Astex Pharmaceuticals (eg, subjects' signed informed consent), in strict confidence.

14.2.4 Source Documentation

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

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

- All relevant observations and data on the condition of the subject throughout the study.

14.2.5 Records Retention

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

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

14.3 Clinical Trial Insurance

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

14.4 Study Administrative Letters and Protocol Amendments

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

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 in the study shall be listed as lead authors on manuscripts and reports of study results. In addition, other than clinical pharmacology studies in healthy volunteers or Phase 1 studies, all clinical studies must be registered with ClinicalTrials.gov.

16.0 REFERENCES

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