Official Title:	**A Phase 3, Randomized, Open-Label, Crossover Study of ASTX727 (Cedazuridine and Decitabine Fixed-Dose Combination) versus IV Decitabine in Subjects with Myelodysplastic Syndromes (MDS) and Chronic Myelomonocytic Leukemia (CMML)**
NCT Number:	NCT03306264
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Clinical Study Protocol — ASTX727-02

A Phase 3, Randomized, Open-Label, Crossover Study of ASTX727 (Cedazuridine and Decitabine Fixed-Dose Combination) versus IV Decitabine in Subjects with Myelodysplastic Syndromes (MDS) and Chronic Myelomonocytic Leukemia (CMML)

PROTOCOL TITLE PAGE

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Amendment 1.9 UK (23 January 2020)
Amendment 1.10 Czech Republic (24 January 2020)
Amendment 1.11 Canada (19 February 2020)
Amendment 1.12 Canada (08 June 2020)

Amendment 2.0 US (20 January 2021)
Amendment 2.1 Canada (20 January 2021)
Amendment 2.2 Czech Republic (20 January 2021)

PROTOCOL SYNOPSIS

Study Number and Title:
ASTX727-02: A Phase 3, Randomized, Open-Label Crossover Study of ASTX727 (Cedazuridine and Decitabine Fixed-Dose Combination) versus IV Decitabine in Subjects with Myelodysplastic Syndromes (MDS) and Chronic Myelomonocytic Leukemia (CMML)

Investigational Drug: ASTX727 (recently approved as INQOVI®) is a film-coated, oval, immediate-release tablet of a fixed-dose combination (FDC) of cedazuridine (E7727) (100 mg) and decitabine (35 mg) for oral administration.

Clinical Phase: 3

Study Centers Planned/Country: Multicenter, North America

Study Objectives:
Primary Objective
- To establish decitabine AUC equivalence of 5-day dosing between ASTX727 and IV decitabine.

Secondary Objectives
To assess the following:
- Long-term safety and efficacy (response rate) of ASTX727.
- Long interspersed nucleotide elements-1 (LINE-1) demethylation.
- Additional pharmacokinetics (PK) parameters.

Study Design and Investigational Plan:
This is a multicenter, randomized, open-label, 2-period, 2-sequence crossover study of ASTX727 versus IV decitabine. Adult subjects who are candidates to receive IV decitabine will be randomized in a 1:1 ratio to receive the ASTX727 FDC tablet Daily×5 in Cycle 1, followed by IV decitabine 20 mg/m^2 Daily×5 in Cycle 2, or the converse order. Adequate PK assessments from both cycles will be required for subjects to be evaluable for analysis of the primary endpoint. After completion of the first 2 treatment cycles, subjects will continue to receive treatment with ASTX727 in 28-day cycles until disease progression, unacceptable toxicity, or the subject decides to discontinue treatment or withdraw from the study.

***Study Population**:*
Inclusion Criteria
Approximately 132 (at least 118 evaluable) subjects will be enrolled in this study at approximately 60 study centers in North America. Subjects must fulfill all of the following inclusion criteria:

1. Able to understand and comply with the study procedures, understand the risks involved in the study, and provide legally effective informed consent before the first study-specific procedure; specifically able to comply with the PK assessment schedule during the first 2 treatment cycles.
2. Men or women ≥18 years who are candidates to receive IV decitabine, ie, subjects with MDS previously treated or untreated with de novo or secondary MDS, including all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia [CMML]), and subjects with MDS International Prognostic Scoring System (IPSS) int-1, -2, or high-risk MDS.
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
4. Adequate organ function defined as follows:
   a) Hepatic: Total or direct bilirubin ≤2 × upper limit of normal (ULN); AST/SGOT and ALT/SGPT ≤2.5 × ULN.
   b) Renal: serum creatinine ≤1.5 × ULN or calculated creatinine clearance or glomerular filtration rate >50 mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal.
5. No major surgery within 30 days of first study treatment.
6. Life expectancy of at least 3 months.
7. Women of child-bearing potential must not be pregnant or breastfeeding and must have a negative pregnancy test at screening. Women of non-childbearing potential are those who have had a hysterectomy or bilateral oophorectomy, or who have completed menopause, defined as no menses for at least 1 year AND either age ≥65 years or follicle-stimulating hormone levels in the menopausal range.
8. Subjects and their partners with reproductive potential must agree to use effective contraceptive measures during the study and for 3 months after the last dose of study treatment. Effective contraception includes methods such as oral contraceptives or double-barrier method (eg, use of a condom AND diaphragm, with spermicide).

Exclusion Criteria

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

1. Prior treatment with more than 1 cycle of azacitidine or decitabine.
2. Hospitalization for more than 2 days for documented febrile neutropenia, pneumonia, sepsis, or systemic infection in the 30 days before screening.
3. Treatment with any investigational drug or therapy within 2 weeks of study treatment, or 5 half-lives, whichever is longer, before the first dose of study treatment, or ongoing clinically significant adverse events (AEs) from previous treatment.
4. Cytotoxic chemotherapy or prior azacitidine or decitabine within 4 weeks of first dose of study treatment.
5. Concurrent MDS therapies, including lenalidomide, erythropoietin, cyclosporine/tacrolimus, granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor, etc. (Prior treatment with these agents is permitted, provided that completion is at least 1 week before the first dose of study treatment.)
6. Poor medical risk because of other conditions such as uncontrolled systemic diseases, active uncontrolled infections, or comorbidities that may put the patient at risk of not being able to complete at least 2 cycles of treatment.
7. 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.
8. Rapidly progressive or highly proliferative disease (total white blood cell count of $>15 \times 10^9$/L) or other criteria that render the subject at high risk of requiring intensive cytotoxic chemotherapy within the next 3 months.
9. Life-threatening illness or severe organ system dysfunction, such as uncontrolled congestive heart failure or chronic obstructive pulmonary disease, or other reasons including laboratory abnormalities, which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ASTX727, or compromise completion of the study or integrity of the study outcomes.
10. Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, prostate cancer or breast cancer under control with hormone therapy, or other cancer from which the subject has been disease free for at least 2 years.
11. Hypersensitivity to decitabine, cedazuridine, or any of the excipients in ASTX727 tablets or IV decitabine.

Study Treatment:

Investigational medicinal product (IMP): ASTX727 tablet with ~240 mL (8 fluid oz) water Daily×5 every 28 days. Subjects must fast from food (clear liquids are allowed) 2 hours before and 2 hours after administration. No adjustment of dose for weight or body surface area will be made.

Reference product: IV decitabine 20 mg/m^2 as a 1-hour IV infusion Daily×5.

Study Endpoints:

Primary Endpoint

Comparison between ASTX727 and IV decitabine:

- Total 5-day AUC exposures of decitabine after treatment with ASTX727 versus IV decitabine.

Secondary Endpoints

- Safety as assessed by AEs, concomitant medications, physical examination, clinical laboratory tests (hematology and serum chemistry), vital signs, ECOG performance status, and electrocardiogram (ECG).
- Maximum %LINE-1 demethylation.
- Additional secondary PK parameters.
- Clinical response (complete response [CR], marrow complete response [mCR], partial response (PR), and hematologic improvement [HI]) based on International Working Group (IWG) 2006 MDS response criteria.
- Red blood cell (RBC) or platelet transfusion independence (TI).
- Leukemia-free survival, defined as the number of days from the date of randomization to the date when bone marrow or peripheral blood blasts reach ≥20%, or death from any cause.
- Overall survival (OS), defined as the number of days from the date of randomization to the date of death from any cause.

Study Assessments and Procedures:
Study evaluation visits will occur on Days 1-5, then weekly, in Cycles 1 and 2. Bone marrow samples will be collected from subjects at Screening or within 21 days before Cycle 1 Day 1; on or before Day 1 of Cycles 3, 5, and 7, then every 3 months in first year and every 6 months thereafter. A manual differential of the myeloid cells in bone marrow will be performed with a minimum of 100 cells counted and a specific myeloblast percent generated. Complete blood count and differential will be obtained weekly during Cycles 1 and 2 then biweekly in Cycles ≥3, with specific output being hemoglobin, platelet count, white blood cell count and percent neutrophils (percent polymorphonuclear neutrophils and bands) or an absolute neutrophil count, and percentage of blasts. QTc interval will be assessed via routine ECG at Screening and on Day 3 of Cycles 1 and 2. The severity (intensity) of AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) for Cancer Clinical Trials, version 4.03.

Pharmacokinetics Assessments:
The schedule for PK assessments in Cycles 1 and 2 is as follows:

- ASTX727 cycle: predose on Days 1 through 5; serial collections on Days 1, 2, and 5; collection on Day 3 at 3 hours.
- IV decitabine cycle: predose on Days 1 and 5; serial collections on Days 1 and 5; collection on Day 3 before end of infusion.

Efficacy Assessments:
Peripheral blood and bone marrow aspirate or biopsy will be collected and used for response assessments and assessment of leukemic transformation. Bone marrow aspirate or biopsy will be performed at Screening (or within 21 days before Cycle 1 Day 1), on or before Day 1 of Cycles 3, 5, 7, then every 3 months during the first year and every 6 months thereafter. Transfusion (blood and platelet) requirements will be recorded monthly. Survival status will be monitored and documented throughout the study.

Pharmacodynamic Assessments
LINE-1 methylation (in blood) will be measured at the following time points:

- Predose on Day 1 of Cycles 1, 2, and 3.
- Days 8, 15, 22 of Cycles 1 and 2.

Safety Assessments:
Safety will be assessed by subject reported and investigator observed AEs, along with concomitant medications, physical examination, clinical laboratory tests (hematology, serum chemistry, urinalysis), vital signs, ECOG performance status, and ECG.

Sample Size and Statistical Analyses:
Sample Size Calculation:
In a standard 2-period, 2-sequence crossover design under a 1:1 randomization ratio, all treated subjects with sufficient PK data will be included in the Primary Endpoint PK Analysis Set. Complete PK will require subjects to be successfully dosed and samples to be correctly collected and tested from a minimum of Day 1 and Day 2 or 5 in the ASTX727 cycle, and Day 1 or 5 in the IV decitabine cycle. The 5-day AUC will be calculated from all complete PK data sets in a cycle. A total of 118 subjects in the Primary Endpoint PK Analysis Set included in the 2 one-sided equivalence tests for the geometric mean ratio of ASTX727 5-day AUC relative to IV decitabine 5-day AUC will provide 90% power at the statistical significance level of 0.05, when the true ratio of geometric means is 1.0, the coefficient of variation (CV) under an unlogged scale is 0.55, and the 90% confidence interval (CI) equivalence limits for the ratio of geometric means are 0.8 and 1.25. Assuming 10% of subjects may not be evaluable in the study, approximately 132 subjects will need to be randomized.

Primary Pharmacokinetics Endpoint Analysis:
The primary endpoint analysis will include data from the following time points to calculate 5-day AUC:

- ASTX727 AUC: Days 1, 2, and 5.
- IV decitabine AUC: Days 1 and 5.

PK exposure parameters will be estimated for all PK-evaluable subjects based on noncompartmental analysis. The primary endpoint of decitabine 5-day AUC will be analyzed in the log scale using the mixed effect model including fixed effects of sequence, period, and treatment, and a random effect of subject within sequence. A 90% CI for the geometric mean ratio of decitabine 5-day $AUC_{0\text{-}t}$ will be obtained by applying the exponential function on the 2-sided 90% CI for the difference of mean decitabine 5-day AUC between ASTX727 and IV decitabine in

the log scale from the mixed effect model. The study will be claimed positive if the 90% CI for the geometric mean ratio is contained within the interval (0.8, 1.25).

Secondary Endpoint Analyses:

Safety

The Safety Analysis Set will include all subjects who received any amount of study treatment. Safety will be assessed by incidence, grade, and seriousness of AEs. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) for Cancer Clinical Trials version 4.03. Treatment exposure, AEs including relatedness and severity, serious AEs (SAEs), and reasons for treatment discontinuation will be summarized. Concomitant medication will be coded using the WHO Drug Dictionary.

Efficacy

Efficacy endpoints will be analyzed for subjects in the Efficacy Analysis Set, defined as the set of all subjects who received at least one full dose (day) of study treatment. Proportions of clinical responses will be calculated for subjects in the Efficacy Analysis Set, while TI rates will be calculated based on subjects who are transfusion dependent at baseline. The 95% Wald CIs will be provided for clinical response rates and TI rates. Leukemia-free survival and OS will be presented using Kaplan-Meier estimates along with 95% CIs for medians.

Pharmacokinetics

Decitabine PK parameters $AUC_{0\text{-}inf,}$ C_{max}, T_{max}, apparent clearance (CL/F), apparent volume of distribution (Vd/F), and apparent half-life ($t_{1/2}$) are of secondary interest and will be reported with $AUC_{0\text{-}t}$ where applicable. The PK parameters of cedazuridine and cedazuridine-epimer will be also reported. The secondary endpoint analysis will also include population PK for evaluation of various covariates and exposure-response.

Pharmacodynamics

All treated subjects with evaluable %LINE-1 data will be included for analysis. Evaluable pharmacodynamic (PD) samples will include Day 1 and at least Day 8 or Day 15 methylation results. To avoid the confounding effects of differing baselines in Cycle 2 vs Cycle 1 observed in study ASTX727-01, subjects will be compared for each of the 2 cycles separately, thus limiting the evaluation to interpatient comparisons in each of the 2 cycles. The 95% CI for the difference of mean maximum %LINE-1 demethylation between ASTX727 and IV decitabine in Cycle 1 will be generated using an analysis of variance (ANOVA) model. The 95% CIs for the maximum %LINE-1 demethylation will also be generated for ASTX727 and IV decitabine, respectively.

Study Duration and Termination:

The expected study duration is approximately 18 months (12 months of enrollment and at least 6 months of treatment and follow up). The primary analysis will be conducted after all subjects complete the first 2 cycles.

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
AE	adverse event
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ANOVA	analysis of variance
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
BLQ	below the limit of quantitation
CBC	complete blood count
CDA	cytidine deaminase
CDAi	CDA inhibitor
cedazuridine	International Nonproprietary Name for E7727
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	clearance
C_{max}	maximum concentration
CMML	chronic myelomonocytic leukemia
CRF/eCRF	case report form/electronic case report form
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome P450
DAC	Dacogen®
DNMT	DNA methyltransferase
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EMEA	European Agency for the Evaluation of Medicinal Products
FDA	Food and Drug Administration
FDC	fixed-dose combination
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
HDPE	high density polyethylene
HI	hematologic improvement
HI-E	erythroid response
HI-N	neutrophil response
HI-P	platelet response
HMA	hypomethylating agent
IB	Investigator Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ID	identification
IEC	Independent Ethics Committee
IMP	investigational medicinal product (the specific Astex drug product under study)
IND	Investigational New Drug
int	intermediate
IPSS	International Prognostic Scoring System

IRB	Institutional Review Board
IV	intravenous
IWG	International Working Group
LINE-1	long interspersed nucleotide elements-1
mCR	marrow complete response
MDS	myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	multiple gated acquisition scan
NCE	new chemical entity
NCI	National Cancer Institute
OS	overall survival
PD	pharmacodynamic(s)
PE	physical examination
PK	pharmacokinetic(s)
PR	partial response
PT	Preferred Term
RBC	red blood cell
SAE	serious adverse event
SOC	System Organ Class
SD	standard deviation
SSC	Study Steering Committee
SUSAR	serious unexpected suspected adverse reaction
$t_{1/2}$	half life
TEAE	treatment-emergent adverse event
TI	transfusion independence
t_{max}	time to reach maximum concentration
ULN	upper limit of normal
US	United States
USA	United States of America
Vd/F	apparent volume of distribution
WHO	World Health Organization

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

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 and associated with cytopenias affecting one or more of the three lineages (Bennett 1982; Cheson et al 2000; Heaney and Golde 1999; Kantarjian and Estey 2001). Most MDS patients are elderly, and their prognosis (with high-risk factors) is poor (Garcia-Manero 2015). Patients often present with complications related to anemia (fatigue), neutropenia (infections), or thrombocytopenia (bleeding). In addition, variable blast expansion, and, less commonly, leukocytosis are observed. MDS may evolve into acute myeloid leukemia (AML) in 10% to 70% of patients.

Prognosis for MDS patients is poor: 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.

Based on the IPSS scoring system, patients with lower risk (IPSS low risk or intermediate [int]-1) MDS (approximately 70% of patients) have an expected median survival of 3.5 to 5.7 years. Median survival for higher risk patients (int-2 and high-risk MDS) ranges from 0.4 to 1.2 years (Greenberg et al 1997).

1.2 Background of Treatment Options

Hypomethylating agents (HMAs), such as decitabine and azacitidine, are effective treatment modalities for hematologic cancers and are FDA-approved for higher risk MDS and chronic myelomonocytic leukemia (CMML). HMAs have also shown promising clinical activity in AML. Consecutive daily dosing for 5 or 7 days in 28-day cycles are the approved schedules. Continued monthly treatment for patients who respond is now the standard of care to avoid early relapse (Cabrero et al 2015). Treatment, which may continue for several months or even years, may engender significant hardship due to the 5 to 7 daily visits required each month, and the 1-hour intravenous (IV) infusion or large-volume subcutaneous injections. A possible consequence is non-compliance or premature discontinuation. Development of a formulation for convenient oral administration of HMAs has proven difficult due to rapid metabolism by cytidine deaminase (CDA) during passage through the gastrointestinal (GI) mucosa and liver. To achieve even modest

exposures of drug requires administration of large doses, which are associated with Grades 3 and 4 GI toxicity (nausea, vomiting, and diarrhea) and high variability in exposures (Garcia-Manero et al 2011). Successful development of an oral HMA will alleviate the significant inconvenience of long-duration parenteral therapy, particularly for those patients who may benefit most.

1.3 Background of ASTX727

Astex Pharmaceuticals has developed an oral drug product, ASTX727 (recently approved as INQOVI® [current INQOVI Prescribing Information]), which is composed of the new chemical entity (NCE) cedazuridine (E7727; 100 mg), a CDA inhibitor (Ferraris et al 2014), and 35 mg decitabine. In animal models, dose-dependent increases in decitabine exposures were achieved when increasing doses of cedazuridine were administered with oral decitabine (refer to the ASTX727 Investigator Brochure [IB]). This interaction effect was demonstrated in CD2F1 mice, rhesus monkeys, and in cynomolgus monkeys, supporting the mechanism of action of improved pharmacokinetics (PK) for the combination of cedazuridine with oral decitabine. Because cedazuridine inhibits CDA in the gut and liver, ASTX727 reduces first pass metabolism of decitabine thus enhancing the bioavailability of decitabine and achieving exposure and hypomethylation activity similar to IV decitabine at the currently approved dosing schedule of 20 mg/m^2 Daily×5. Decitabine was approved in 2006 by the United States Food and Drug Administration (US FDA) as Dacogen® (decitabine) (current Dacogen Prescribing Information), administered as a 1-hour IV infusion for the treatment of higher risk patients with MDS and CMML.

Decitabine is a cytidine analog that profoundly inhibits DNA methylation by incorporating into DNA and subsequently forming covalent bonds with DNA methyltransferase (DNMT) (Issa and Kantarjian 2009). This enzyme deficiency renders the cell unable to maintain DNA methylation after cellular replication, resulting in effective DNA demethylation and re-expression of previously silenced genes. The analysis of the methylation of repetitive genomic elements, as in the long interspersed nucleotide elements (LINE-1) that are normally heavily methylated, represents a pharmacodynamic surrogate marker for global DNA methylation (Yang et al 2004).

The Astex ASTX727 program's completed Phase 1-2 first-in-human trial, ASTX727-01, was a PK-guided dose escalation and dose confirmation study of ASTX727 in patients with MDS and CMML intended to define appropriate doses of the individual components of ASTX727 (cedazuridine + decitabine) so that decitabine exposure after oral administration of ASTX727 is comparable to exposure after IV decitabine at the approved daily dose of a 1-hour infusion at 20 mg/m^2. Results showed that ASTX727 enables therapeutic dose-dependent increases in decitabine exposure to therapeutic levels and achieves demethylation and clinical activity comparable to IV decitabine at the FDA approved 5-day dose regimen using fixed doses of 35 mg decitabine and 100 mg cedazuridine (Garcia-Manero 2016, Garcia-Manero et al 2020; current Dacogen Prescribing Information).

The main purpose of the current study is to demonstrate AUC equivalence of ASTX727 to IV decitabine.

1.4 Summary of Nonclinical and Preliminary Clinical Data for ASTX727

1.4.1 General Information

General information on ASTX727 is located in Section 7.1 of this protocol. ASTX727 is an oral fixed-dose combination tablet containing cedazuridine (E7727, a CDA inhibitor) and decitabine.

1.4.2 Nonclinical Data

Refer to the ASTX727 IB for more detailed nonclinical information on the components of ASTX727 (cedazuridine + decitabine). A summary is given below.

In vitro safety pharmacology studies performed with various concentrations of cedazuridine are summarized in Table 1.

Table 1: Summary of Cedazuridine (E7727) In Vitro Pharmacology Studies

Title	System	Key Findings for Cedazuridine (E7727)
Effect of E7727 on the Half-life of Gemcitabine in the Presence of CDA in 100 mM pH 7.4 Tris-HCl Buffer at 37°C	Stability study	Gem $T_{½}$ +CDA ≤36 min Gem $T_{½}$ +CDA +E7727 ≥66 h
Determination of IC_{50} and Binding Constant (Ki) of MGI 25208	Human recombinant CDA	IC_{50} = 400 nM, Ki = 400 nM
Determination of E7727 and ER-876437 IC_{50} against human recombinant Cytidine Deaminase (CDA)	Human recombinant CDA	IC_{50} = 281 ± 100 nM
Measurement of antiproliferative activity of E7727 in HCC827, NCI-H820, NCI-H1650, EVSA-T, MDA-MB-231, HCT-116, HL60, and THP-1 cell lines	Human cell lines	No significant inhibition of any cell line tested

In vivo pharmacology studies performed to determine the effect of cedazuridine on anticancer activity of oral decitabine are summarized in Table 2.

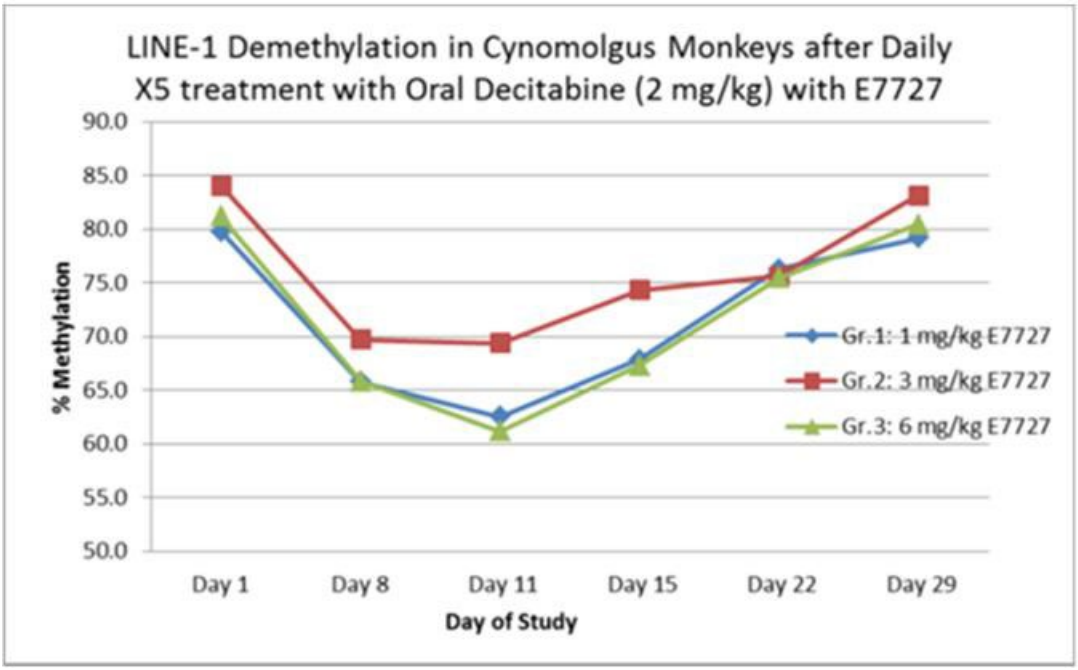
Table 2: Summary of Cedazuridine (E7727) In Vivo Pharmacology Studies

Title	System	Key Findings for Cedazuridine (E7727)
Effect of E7727 on in vivo anticancer activity of oral decitabine against CD2-F1 mouse L1210 disseminated model	L1210 mouse ALL disseminated model	All 3 dose levels of E7727 (1, 10, and 100 mg/kg) + 0.4 mg/kg oral decitabine have significant antitumor activity
Effect of E7727 on in vivo anticancer activity of oral decitabine against KG-1 human AML disseminated model	KG-1 human AML disseminated model	All 3 doses of E7727 (1, 10, and 100 mg/kg) + 0.3 mg/kg oral decitabine have significant antitumor activity

The pharmacodynamics (PD) of oral decitabine + cedazuridine were demonstrated in a one-cycle study in cynomolgus monkeys in which decitabine was administered at 2 mg/kg with cedazuridine doses of 1, 3, or 6 mg/kg Daily×5, followed by 23 days of no dosing. Demethylation of LINE-1

sequences was seen for all 3 treatment groups, with the maximum demethylation of -17.4% to -24.5% achieved at Day 11.

Figure 1: LINE-1 Demethylation in Cynomolgus Monkeys – Cedazuridine (E7727) + Oral Decitabine: Three Dose Groups Daily×5 at 2 mg/kg



Source: Oganesian et al 2013.

Safety pharmacology studies conducted to date do not highlight an off-target concern for cardiovascular or other organ systems.

1.4.3 Clinical Data and Human Pharmacokinetics

Refer to the ASTX727 IB for more detailed clinical information. A summary is given below.

In the Phase 1 (dose escalation) part of study ASTX727-01, oral cedazuridine and decitabine were administered concomitantly and each escalated separately to identify a dose combination that delivers oral decitabine AUC similar to that for 1-hour IV decitabine infusion at 20 mg/m^2. Five different dose combinations were evaluated, with Cohort 4 (100 mg cedazuridine and 40 mg decitabine) achieving 144% of IV decitabine AUC, while the Cohort 5 expansion at 100 mg cedazuridine and 30 mg decitabine produced 85% of IV decitabine AUC (Table 3).

Table 3: Decitabine AUC – Dose Escalation Stage (Phase 1) of ASTX727-01

Subjects Who Completed Cycle 1 (N=43); Data are Geometric Mean (CV%)										
	Oral Dose[a] (mg)			AUC_{last} by Day (ng*h/mL) Geometric Mean (CV%)				5-Days Total AUC_{last}		% of AUC
Cohort	DAC	cedazuridine	N	D −3	D2	D5	IV D1	Oral	IV	(Oral/IV)
1	20	40	6	11.4 (98)	46.8 (139)	74.0 (95)	174 (51)	345	872	40
			5[b]	8.67 (50)	32.0 (60)	56.7 (36)	151 (38)	260	753	35
2	20	60	6	8.21 (63)	32.8 (47)	77.5 (33)	180 (34)	346	899	39
3	20	100	6	8.72 (75)	57.5 (51)	106 (46)	198 (40)	482	992	49
4	40	100	6	32.2 (73)	175 (46)	234 (59)	155 (44)	1120	775	144
5	30	100	19[c]	16.8 (66)	87.3 (65)	153 (50)	170 (35)	701	852	85

DAC=Dacogen

[a] Oral dosing was not body weight or body surface area adjusted. IV dose was 20 mg/m^2 in all cohorts.

[b] Data presented with one subject in Cohort 1 excluded as an extreme outlier.

[c] IV used n=18 as one subject was excluded as an extreme outlier.

Source: DE DAC AUC_{last}_(n=43 and n=42 w Cht1=5)_EOP.

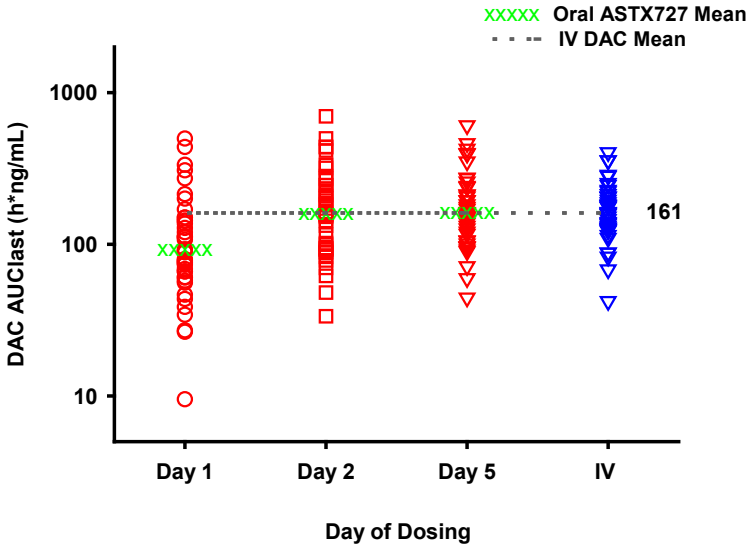
Based on this outcome, a dose combination of 100 mg cedazuridine with 35 mg decitabine (ie, intermediate dose between 30 mg and 40 mg) was selected for the Phase 2 randomized, crossover (dose confirmation) stage, wherein full-cycle AUC exposures from oral ASTX727 were compared with full-cycle IV AUC. Based on data from 43 subjects, ASTX727 achieved 95.5% of IV AUC and met the equivalence test based on a 90% confidence interval (CI) and margins of 0.8-1.25 (Table 4 and Figure 2).

Table 4: AUC Equivalence Analysis Based on 5-Day AUC Estimates – Dose Confirmation Stage (Phase 2) of ASTX727-01

				Ratio of Adjusted Geometric Means	
Population	N	Treatment	Adjusted Geometric Means	Estimate	90% Confidence Interval
PK Analysis Set	43	cedazuridine + decitabine	769.194	0.955	(0.806, 1.133)
		IV decitabine	805.130	--	

Source: PK_Bioavailability.rtf.

Figure 2: **Individual and Mean Decitabine AUC after ASTX727 Administration or IV Decitabine Infusion (N=43) – Dose Confirmation Stage (Phase 2) of ASTX727-01**



Source: DC DAC AUC (n=43)_by Day_EOP_Fig 12.

After dosing with ASTX727, decitabine AUC exposures were higher on Days 2-5 vs Day 1 of dosing. However, Day 5 decitabine exposures appeared to be the same as on Day 2; this was consistent with the similar and consistent presence of trough cedazuridine levels predose on Days 2 through 5, which also explains the lower exposure on Day 1 due to absence of any cedazuridine exposure before the first dose of ASTX727. To account for the lower exposures on Day 1, the estimated total AUC from 5 days of dosing with IV decitabine was compared with the AUC from 5 days of dosing with ASTX727 imputed from a 5-day model.

The variability of decitabine AUC exposures was slightly higher after administration of the oral combination, compared with IV infusion. This was expected, as IV dosing is adjusted for body surface area, whereas the oral dose was fixed for all subjects regardless of body weight. Despite the somewhat higher variability for decitabine AUC after the oral combination, the AUC equivalence analysis showed that the oral combination achieved a mean decitabine AUC ratio of 0.955 with the 90% CI of 0.806, 1.133 based on N=43 subjects.

Recently, the first PK analysis from Phase 3 study ASTX727-02 based on 123 treated subjects with MDS and CMML with complete PK data was presented. PK data from the first 2 cycles comparing oral ASTX727 to IV decitabine showed 5-day cycle decitabine $AUC_{0\text{-}24}$ oral/IV ratio of 98.9% with a very narrow 90% CI of 92.7% to 105.6%, confirming equivalent decitabine exposure between oral and IV with high confidence (Garcia-Manero et al 2019). There were no subjects in whom there was no systemic decitabine exposure after oral ASTX727.

1.5 Summary of Data for Other Study Treatment

The comparator product to be used in this trial is IV decitabine, for which the mechanism of action, prescribing information, and critical clinical data are provided in the FDA-approved Dacogen package insert (current Dacogen Prescribing Information).

1.6 Potential Risks and Benefits to Human Subjects

No safety issues have been identified to date with ASTX727 that are inconsistent with the safety profile of IV decitabine. Blood levels of ASTX727 (at 100 mg cedazuridine and 35 mg decitabine) in study ASTX727-01 have been shown to be similar to levels seen after 1-hour IV infusion with 20 mg/m^2 decitabine. Risks of ASTX727 in humans are described further in Section 8.0. For more detailed information, please refer to the IB for ASTX727.

Most cancer patients prefer oral to injectable drug formulations (Liu et al 1997); an oral HMA will alleviate the inconvenience of potential long-duration parenteral therapy as well as the hardship involved with the clinic visits associated with a drug that must be administered intravenously. This is of particular importance considering the prevalence of this disease in the elderly and the need for continued monthly treatment potentially for years, particularly for those patients who respond to treatment and benefit the most. An oral drug may also improve compliance with 5 days/month treatment.

2.0 RATIONALE

2.1 Rationale for the Study

This Phase 3 study will establish AUC equivalence of ASTX727 to IV decitabine in a randomized, crossover design in approximately 118 evaluable subjects comparing 5-day AUC from Cycle 1 and Cycle 2 as the primary endpoint. Preliminary data from study ASTX727-01 show that ASTX727 enhances oral bioavailability of decitabine, permitting the achievement of exposures similar to IV decitabine at the currently approved dosing schedule of 20 mg/m^2 Daily×5 using similar doses of oral decitabine (35 mg).

2.2 Rationale for ASTX727 Dose and Regimen

Data from the Dose Escalation Stage (Phase 1) of study ASTX727-01 show that a fixed dose of 100 mg cedazuridine, and decitabine doses of 30 mg and 40 mg, achieved an AUC of 85% and 144% respectively of that of IV decitabine over 5 days of dosing (Table 3). The Dose Confirmation Stage (Phase 2) was therefore conducted using the combination of cedazuridine 100 mg with decitabine 35 mg as an intermediate dose between the 30 mg and 40 mg evaluated in Phase 1. That dose combination achieved 95% of IV decitabine AUC and reached the 90% equivalence margin of 0.80-1.25 (Table 4). Dosing of ASTX727 in Phases 1 and 2 of study ASTX727-01 was conducted using separate capsules of cedazuridine and decitabine administered concomitantly to titrate dose. A new FDC tablet formulation was manufactured after the doses of the 2 components (100 mg cedazuridine and 35 mg decitabine) were established and is under investigation in Phase 2

of ASTX727-01. A study in cynomolgus monkeys (BioDuro Study Report APL-FFS-PK-20160512-01) has shown that PK data were similar between the FDC tablet and the capsule formulations.

Protocol ASTX727-01 was then amended primarily to confirm the PK data, using the new FDC tablet formulation in 24 subjects using a crossover design (FDC Stage) as in the Dose Confirmation Stage. Preliminary data from the FDC stage of ASTX727-01 show the 5-day AUC ratio of approximately 1.05 between ASTX727 tablets and IV decitabine.

3.0 STUDY OBJECTIVES

3.1 Primary Objective

- To establish decitabine AUC equivalence of 5-day dosing between ASTX727 and IV decitabine.

3.2 Secondary Objectives

To assess the following:

- Long-term safety and efficacy (response rate) of ASTX727.
- LINE-1 demethylation.
- Additional pharmacokinetics (PK) parameters.

4.0 INVESTIGATIONAL PLAN

4.1 Overall Study Design

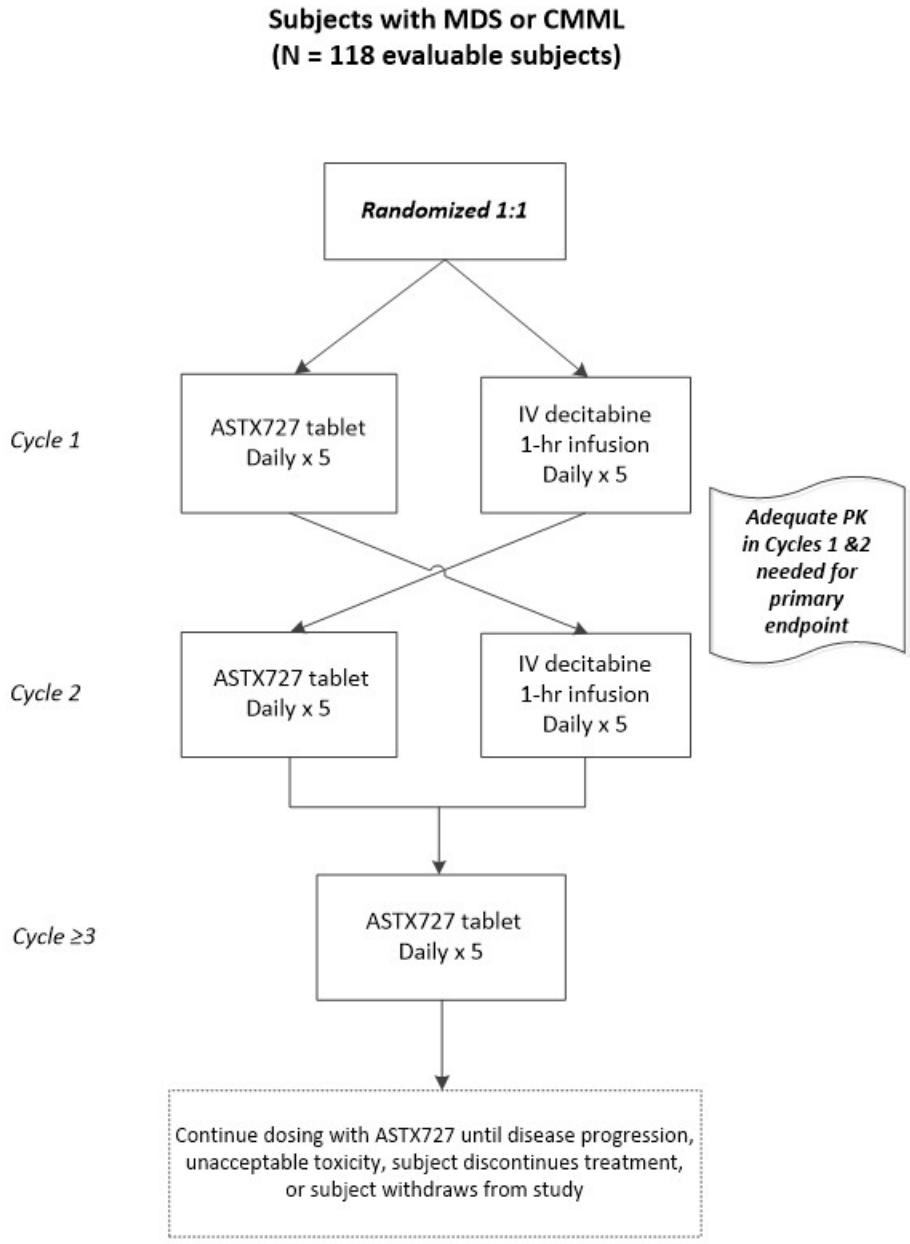
This is a Phase 3, multicenter, randomized, open-label, 2-period, 2-sequence crossover study comparing decitabine AUC equivalence of ASTX727 and IV decitabine. Adult subjects with MDS or CMML who are candidates to receive decitabine will be randomized in a 1:1 ratio to receive the ASTX727 FDC tablet Daily×5 in Cycle 1, followed by IV decitabine 20 mg/m^2 Daily×5 in Cycle 2, or the converse order (Figure 3). Adequate PK assessments from Cycles 1 and 2 will be required for subjects to be evaluable for analysis of the primary endpoint. After completion of the first 2 treatment cycles, subjects will continue to receive treatment with ASTX727 in 28-day cycles until disease progression, unacceptable toxicity, or the subject decides to discontinue treatment or withdraw from the study.

Assessment of efficacy and safety of ASTX727 in the patient population requires multiple cycles and is critical to measure all the secondary clinical endpoints (response rate, transfusion independence, survival, and adverse events). The only way to be able to measure these important clinical endpoints of the study, is for patients to receive ASTX727 from Cycle 3 onwards after completing the PK component in the first 2 cycles.

As of the effective date of this protocol amendment, the COVID-19 health emergency is altering the way clinical studies are being conducted, such that alternative measures are being implemented

to ensure the safety of subjects and maintain the integrity of clinical trial data. Appendix 3 provides information regarding potential modifications to the conduct of the study.

Figure 3: Study Schema



4.2 Discussion of Study Design

The clinical efficacy and safety of decitabine in MDS and CMML have been established previously, with a favorable benefit-risk that led to approval for treatment of these conditions. The approach for establishing the safety and effectiveness of ASTX727 is based on a PK bridging approach in which the primary study endpoint is 5-day cumulative AUC equivalence between ASTX727 and IV decitabine at the approved 5-day dose regimen. Data from study ASTX727-01 showed that similar daily dose exposure profiles between the IV and orally administered drug resulted in similar clinical activity and safety, consistent with the known profile of decitabine IV. Demonstration that the mean 5-day cumulative exposure of decitabine from oral ASTX727 is equivalent to the approved IV regimen would predict similar clinical performance from the two drugs. The crossover design of the first 2 cycles in the current study allows robust PK analysis. The washout period between the 2 cycles (ie, Days 6-28) is appropriate, and no decitabine or cedazuridine is expected to be present predose at Cycle 2 Day 1. Continuation of ASTX727 treatment from Cycle 3 onwards would confirm longer term activity and safety of the oral compound. Assessment of efficacy and safety are not conditional upon achieving the PK primary endpoint in this study, but are an independent component for acquiring data necessary to support marketing application (PK, efficacy, and safety data of ASTX727 at the selected fixed doses of 100 mg cedazuridine and 35 mg decitabine). The treatment of subjects with ASTX727 at the selected doses in this study is supported by data from Phase 1 and Phase 2 (Garcia-Manero et al 2020; Savona et al 2019) that showed that ASTX727 at these doses produce equivalent exposure to IV decitabine at 20 mg/m^2 and achieves comparable efficacy and safety in a Phase 2 study in MDS and CMML.

4.3 Study Endpoints

4.3.1 Primary Endpoint

Comparison between ASTX727 and IV decitabine:

- Total 5-day AUC exposures of decitabine after treatment with ASTX727 versus IV decitabine.

4.3.2 Secondary Endpoints

- Safety as assessed by AEs, concomitant medications, physical examination, clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, and electrocardiogram (ECG).
- Maximum %LINE-1 demethylation.
- Additional secondary PK parameters.
- Clinical response (complete response [CR], marrow complete response [mCR], partial response (PR), and hematologic improvement [HI]) based on International Working Group (IWG) 2006 MDS response criteria.
- Red blood cell (RBC) or platelet transfusion independence (TI).

- Leukemia-free survival, defined as the number of days from the date of randomization to the date when bone marrow or peripheral blood blasts reach ≥20%, or death from any cause.
- Overall survival (OS), defined as the number of days from the date of randomization to the date of death from any cause.

4.4 Study Steering Committee

The Study Steering Committee (SSC) will comprise the principal investigators (or designees), medical monitor, study director, PK director, and other study team members as appropriate and will review available clinical data on a predetermined schedule. The SSC may recommend changes to the study based on emerging data.

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Number of Subjects and Centers

Approximately 132 (at least 118 evaluable) subjects will be enrolled in this study at approximately 60 study centers in North America.

5.2 Inclusion Criteria

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

1) Able to understand and comply with the study procedures, understand the risks involved in the study, and provide legally effective informed consent before the first study-specific procedure; specifically able to comply with the PK assessment schedule during the first 2 treatment cycles.
2) Men or women ≥18 years who are candidates to receive IV decitabine, ie, subjects with MDS previously treated or untreated, with de novo or secondary MDS, including all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and CMML), and subjects with MDS IPSS int-1, -2, or high-risk MDS.
3) ECOG performance status of 0 to 1.
4) Adequate organ function defined as follows:
    a) Hepatic: Total or direct bilirubin ≤2 × upper limit of normal (ULN); AST/SGOT and ALT/SGPT ≤2.5 × ULN.
    b) Renal: serum creatinine ≤1.5 × ULN or calculated creatinine clearance or glomerular filtration rate >50 mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal.
5) No major surgery within 30 days of first study treatment.
6) Life expectancy of at least 3 months.

7) Women of child-bearing potential must not be pregnant or breastfeeding and must have a negative pregnancy test at screening. Women of non-childbearing potential are those who have had a hysterectomy or bilateral oophorectomy, or who have completed menopause, defined as no menses for at least 1 year AND either age ≥65 years or follicle-stimulating hormone levels in the menopausal range.
8) Subjects and their partners with reproductive potential must agree to use effective contraceptive measures during the study and for 3 months after the last dose of study treatment. Effective contraception includes methods such as oral contraceptives or double-barrier method (eg, use of a condom AND diaphragm, with spermicide).

5.3 Exclusion Criteria

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

1) Prior treatment with more than 1 cycle of azacitidine or decitabine.
2) Hospitalization for more than 2 days for documented febrile neutropenia, pneumonia, sepsis, or systemic infection in the 30 days before screening.
3) Treatment with any investigational drug or therapy within 2 weeks of study treatment, or 5 half-lives, whichever is longer, before the first dose of study treatment, or ongoing clinically significant adverse events (AEs) from previous treatment.
4) Cytotoxic chemotherapy or prior azacitidine or decitabine within 4 weeks of first dose of study treatment.
5) Concurrent MDS therapies, including lenalidomide, erythropoietin, cyclosporine/tacrolimus, granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor, etc. (Prior treatment with these agents is permitted, provided that completion is at least 1 week before the first dose of study treatment.)
6) Poor medical risk because of other conditions such as uncontrolled systemic diseases, active uncontrolled infections, or comorbidities that may put the patient at risk of not being able to complete at least 2 cycles of treatment.
7) 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.
8) Rapidly progressive or highly proliferative disease (total white blood cell count of $>15 \times 10^9$/L) or other criteria that render the subject at high risk of requiring intensive cytotoxic chemotherapy within the next 3 months.
9) Life-threatening illness or severe organ system dysfunction, such as uncontrolled congestive heart failure or chronic obstructive pulmonary disease, or other reasons including laboratory abnormalities, which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ASTX727, or compromise completion of the study or integrity of the study outcomes.

10) Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, prostate cancer or breast cancer under control with hormone therapy, or other cancer from which the subject has been disease free for at least 2 years.

11) Hypersensitivity to decitabine, cedazuridine, or any of the excipients in ASTX727 tablets or IV decitabine.

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.

Astex Pharmaceuticals may stop the study at any time. In this event, Astex will make reasonable efforts to ensure subjects are appropriately transitioned off study.

5.4.1 Discontinuation from Study Treatment

Contact the Astex medical monitor before discontinuing treatment for a given subject.

Subjects who discontinue study treatment at any time will be followed for safety (Section 10.2).

Subjects will be followed for survival/conversion to AML according to Section 9.5.6.

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

Notwithstanding the above, every attempt should be made for subjects to complete at least the first 2 cycles of treatment and the corresponding PK assessments to minimize the number of non-evaluable subjects and safeguard the integrity of the study primary endpoint.

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).

5.4.2 Withdrawal from the Study

Subjects may withdraw consent for the study at any time; the specific reason for withdrawal must be obtained. It is important to obtain follow-up information, according to standard medical practice, on any subject who prematurely withdraws from the study. Every effort must be made to obtain at least the assessments that are critical for efficacy or safety evaluation (eg, disease response, survival, safety assessments), unless the subject withdraws consent from further follow up.

5.4.3 Replacement of Subjects

Enrollment of subjects will continue until the required number of 118 evaluable subjects is reached.

6.0 ENROLLMENT, RANDOMIZATION, AND BLINDING PROCEDURES

After providing legally effective informed consent, subjects will be screened at each study center for assessment of study eligibility. Eligibility will be further confirmed by the medical monitor prior to randomization of the subject. At screening, each subject will be assigned a unique number (subject identification [ID] number) consisting of 6 digits; the first 3 digits will reflect the study center number, followed by a 3-digit number corresponding to the individual subject. The ID will be used to identify the subject throughout the study and will be entered on all study documents.

6.1 Randomization

Eligible subjects will be randomly assigned to Cycle 1 study treatment in a ratio of 1:1 to receive ASTX727 or IV decitabine. Subjects will cross over to the other therapy in Cycle 2. Treatment assignment will be determined through a computer-generated randomization schedule and accessed through an interactive voice response system. Subjects should receive study treatment as soon as possible after randomization.

6.2 Blinding

This is an open-label study. Treatment assignment will be unblinded.

7.0 STUDY TREATMENTS

7.1 Investigational Medicinal Product (IMP) – ASTX727

ASTX727 (recently approved as INQOVI®) is a film-coated, oval, immediate-release FDC tablet containing the combination of cedazuridine (100 mg) and decitabine (35 mg) for oral administration. The tablets are packed as a 5-count in an opaque high-density polyethylene (HDPE) bottle with a child resistant closure. Please see the ASTX727 IB and Pharmacy Manual (provided by Astex) for more information.

7.2 IV Decitabine

Decitabine, 20 mg/m^2 IV will be used as the reference product. Decitabine is approved for IV infusion in the US and will be sourced locally at the US study centers. Decitabine for IV infusion will be provided by the sponsor as an IMP in territories where it is not currently approved for use.

7.3 Study Treatment Storage

ASTX727 tablets should be stored on site as indicated in the study-specific Pharmacy Manual according to institutional policy and the Sponsor's requirements. ASTX727 tablets for outpatient administration should be dispensed by the study pharmacist according to institutional policy and

in accordance with the Sponsor's requirements. Instructions regarding transport from pharmacy to home and at-home storage instructions should be given to the study subject, as applicable.

Decitabine should be stored according to institutional policy and storage instructions provided in the US product package insert (current Dacogen Prescribing Information).

Records of the receipt and dispensing of study 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 drug supplies.

7.4 Study Treatment Administration

The dosing regimen for this study is shown in Table 5. Subjects will receive the ASTX727 FDC tablet Daily×5 in Cycle 1, followed by a 1-hour infusion of IV decitabine 20 mg/m^2 Daily×5 in Cycle 2, or the converse order. In Cycles ≥3, subjects will receive the ASTX727 tablet Daily×5 in 28-day cycles.

Reconstitution of decitabine for IV administration will be performed by the institutional pharmacists according to the US package insert.

Subjects will be required to fast from food for 4 hours on days in all cycles when receiving ASTX727. Fasting begins at least 2 hours prior to and ends 2 hours after dosing. Subjects will take ASTX727 with ~240 mL (8 fluid oz) of water. Clear liquids such as water, black coffee, or tea may be allowed as desired together with any concomitant medication that is needed to be given to the subject. ASTX727 should be taken at the same time of day (8 AM ±1 hour) on each dosing day during the first 2 cycles. In subsequent cycles, ASTX727 should be taken at the same time of day (±1 hour) on dosing days. For late or missed (or vomited) doses, see Section 7.5.

Table 5: Dosing Schedule by Day and Cycle

Cycle (28 Days)	**1**						**2**						**≥3**					
Cycle Day	**1**	**2**	**3**	**4**	**5**	**6-28**	**1**	**2**	**3**	**4**	**5**	**6-28**	**1**	**2**	**3**	**4**	**5**	**6-28**
If randomized to ASTX727 in Cycle 1, then:																		
ASTX727 tablet	×	×	×	×	×								×	×	×	×	×	
IV decitabine (20 mg/m^2)							×	×	×	×	×							
If randomized to IV decitabine in Cycle 1, then:																		
ASTX727 tablet							×	×	×	×	×		×	×	×	×	×	
IV decitabine (20 mg/m^2)	×	×	×	×	×													

NOTE: On days of ASTX727 administration, subjects should take the FDC tablet at the same time each day ±1 hour (8 AM during the first 2 cycles).

7.5 Late or Missed ASTX727 Doses

7.5.1 Cycle 1 or 2

In the ASTX727 cycle (1 or 2), subjects should take the FDC tablet at the same time of day (8 AM ± 1 hour) on each day of ASTX727 administration. If the tablet is taken within 3 hours after 8 AM, proceed with dosing and PK sample collection (if applicable) according to Table 6. (A dose administered within 3 hours after 8 AM will not be considered a protocol deviation.) If the tablet is taken more than 3 hours after 8 AM, the PK for that day may not be evaluable. Contact the medical monitor for instructions regarding whether the PK sampling schedule may be adjusted on the following days (if applicable).

If the subject vomits within 6 hours after dosing on a dosing day, the PK for that day and the following day (if applicable) may not be evaluable. Contact the medical monitor for instructions regarding whether the PK sampling schedule may be adjusted in remaining days of dosing (if applicable).

7.5.2 Cycles ≥3

If an ASTX727 dose is not taken at the intended time on a dosing day, the dose should be taken immediately if the subject remembers by 6:00 PM that day. After 6:00 PM, the dose should be skipped, and dosing should resume the following day at the intended time. Subjects should complete all 5 daily doses; if a dose is missed, the dosing period will extend by one day for every missed dose to complete the 5 daily doses. A vomited dose should not be retaken. Dosing should resume on the next dosing day and continue for the remaining dosing days in the cycle. If the subject experienced repeated vomiting after dosing in Cycles 1 or 2, a prophylactic antiemetic should be considered for the subsequent cycles.

7.6 Guidelines for Adjusting or Withholding Study Treatment

It is important that Cycles 1 and 2 are given at full dose (safely) to allow for proper assessment of exposure after ASTX727 and IV decitabine administration. Contact the Astex medical monitor if considering reducing the dose in the first 2 cycles.

Dose delays up to 2 weeks for recovery of blood counts from drug-related myelosuppression are acceptable. Delays beyond 2 weeks in the first 2 cycles must be approved by the medical monitor. Subjects whose therapy is interrupted during dosing days of ASTX727 in the first 2 cycles may not be evaluable for assessment of the primary endpoint unless treatment can be restarted on a later date (after agreement by the medical monitor) in a manner that will allow AUC assessment (see Section 11.2.2 and Section 11.6). Dosing should be delayed in the presence of non-hematologic toxicities (serum creatinine equal or greater than 2 mg/dL; SGPT or bilirubin equal or greater than 2 times the ULN), or active or uncontrolled infection until these toxicities are resolved.

Beginning with Cycle 3, dose delays to allow recovery of blood counts from drug-related myelosuppression are allowed at the discretion of the investigator. If there is a need for dose

reduction starting from Cycle 3, ASTX727 treatment may be reduced to 4 days. Additional dose reductions may be applied by further reducing treatment to 3 days. Dose reductions should be considered if myelosuppression is suspected to be drug-related rather than disease-related. Transient reductions in blood counts on Day 15 (expected maximal drug effect) followed by a recovery trend by Day 28 may be indicative of a drug-related effect, whereas stable counts or improvements in counts by Day 15 followed by reduction by Day 28 is indicative of a disease effect that is being improved by the drug on Day 15. In the event of drug-related count suppression, a dose reduction in consultation with the medical monitor may be considered to allow the patient to achieve a complete or partial response.

7.7 Concomitant Treatment

Record on the concomitant medication eCRF all treatments a subject receives, including supportive or palliative treatment whether prescription or over the counter, vitamin and mineral supplements, herbs, and medications taken for procedures (eg, biopsy). Also record antacids, proton pump inhibitors, and H_2 antagonists. Specifically record start/stop dates, name of treatment, and indication for use.

7.7.1 Supportive, Prophylactic, or Other Treatments

The investigator is permitted to perform diagnostic testing and to prescribe supportive treatment(s) at his or her discretion. Appropriate hydration and supportive care (eg, antiemetics and blood and platelet transfusions) may be administered according to study center standards. Ensure the subject is adequately hydrated.

All supportive treatment including units of blood and platelet transfusions must be recorded on the eCRF. Aggressive surveillance, prophylaxis, and the treatment of bacterial, fungal, viral, and opportunistic infections are essential to prevent morbidity and mortality.

Antibiotics may be used to prevent or manage febrile neutropenia according to institutional standard practice. Febrile neutropenia is defined as temperature at least 38.5°C when the absolute neutrophil count (ANC) is <1000 cells/μL. Febrile subjects are to be evaluated by physical examination, complete blood count (CBC) with differential, chest x-ray, urine culture, and blood culture. Subjects with febrile neutropenia or frank infection are to be hospitalized for temporizing antibiotic coverage, consistent with local pathogen sensitivities until an infectious agent is identified. Antibiotic prophylaxis (at least a quinolone unless either medically contraindicated or contrary to institutional standard practice) is strongly recommended for subjects with documented ANC $<0.5\times10^9$/L or expected to experience ANC $<0.5\times10^9$/L for any duration during the first 2 cycles. In subsequent cycles, antibiotic prophylaxis is strongly recommended for subjects expecting to experience ANC $<0.5\times10^9$/L for more than 7 days or per local institutional guidelines. The medical monitor should be consulted in cases where specific antibiotics are contraindicated. Fungal prophylaxis is strongly recommended for subjects expected to experience ANC $<0.5\times10^9$/L for more than 7 days during any cycle or per local institutional guidelines.

Hematopoietic growth factors will not be routinely used. However, short-term use of G-CSF for febrile neutropenia is permitted at the discretion of the treating physician and should be guided by accepted practice or institutional guidelines.

7.7.2 Prohibited Medications

Prohibited concomitant therapies while on study are as follows: chemotherapy, immunotherapy, or any experimental therapy.

Also prohibited are other nucleosides or drugs that are metabolized by CDA (including cytarabine, gemcitabine, azacitidine, vidarabine, zalcitabine, zidovudine, telbivudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, emtricitabine, entecavir, apricitabine, idoxuridine, trifluridine, tenofovir and adefovir).

8.0 RISKS/PRECAUTIONS

Refer to the ASTX727 IB for the most current risks and precautions, as well as a list of AEs considered expected with ASTX727 therapy. As with any IMP, subjects may experience reactions or complications that are unknown and are therefore unpredictable.

8.1 Drug-Drug Interactions

The primary activity of cedazuridine is the inhibition of CDA, which enhances the bioavailability of orally administered decitabine. Therefore, drugs known to be metabolized by CDAs should not be given (such drugs include cytarabine, gemcitabine, azacytidine, vidarabine, zalcitabine, zidovudine, telbivudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, emtricitabine, entecavir, apricitabine, idoxuridine, trifluridine, tenofovir and adefovir) on days when ASTX727 is administered and for 24 hours thereafter. As new agents may come to market during the trial, confer with the medical monitor if questions arise.

ASTX727 is not expected to produce cytochrome P450 (CYP)-mediated drug-drug interaction, as ASTX727 has shown no potential to inhibit or induce human CYP enzymes in vitro.

8.2 Genotoxicity

ASTX727 is shown to be genotoxic, which could cause fetal harm. Therefore, subjects with reproductive potential must use methods of contraception during the study (as described in Section 5.0) and for 3 months after the last dose of study treatment. Subjects should promptly notify the investigator if they, or their partner, become pregnant during this period. If a female subject becomes pregnant during the treatment period, she must discontinue study treatment immediately (see Section 10.2.3).

8.3 Overdose Instructions

Record the actual dose of study treatment 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 SAE criteria (defined in Section 10.1.2) on the SAE form within 24 hours (see Section 10.3). Treat any AE (including SAEs) based on standard care for the specific signs and symptoms.

No data are available regarding overdosage of ASTX727. Based on the clinical experience of decitabine, an overdosage of ASTX727 may result in more profound or prolonged myelosuppression and its consequences such as infection, or bleeding, or GI toxicity, and subjects should be managed accordingly. No antidote has yet been developed for overdose of ASTX727.

9.0 STUDY ASSESSMENTS AND PROCEDURES

9.1 Pharmacokinetics

The schedules for PK assessments during the ASTX727 and IV decitabine cycles are provided in Table 6 and Table 7, respectively. Pharmacokinetics will be evaluated on Days 1 through 5 during the cycle of ASTX727 administration (serial collections on Days 1, 2, and 5, trough levels on Days 1-5, and once on Day 3), and on Days 1, 3, and 5 during the cycle of IV decitabine administration. Adequate PK assessments in both Cycles 1 and 2 (see Section 11.2.2) will be required for subjects to be evaluable for the primary study endpoint.

During the IV decitabine cycle, the contralateral arm should be used for PK blood draws. No blood draws for PK assessments should be done from the arm used for IV decitabine infusion.

Detailed instructions for PK sample collection will be provided separately from the protocol. The total blood volume planned for Cycle 1 + Cycle 2 = ~171 mL. The blood draw schedule may be modified by Astex.

Table 6: Schedule of Pharmacokinetics Assessments – ASTX727 Cycle

	ASTX727 Cycle					
Cycle Day	**1**	**2**	**3**	**4**	**5**	**6-28**
Pre-dose (within 90 min before dosing)	×	×[a]	×[a,b]	×	×	
TIME AFTER ORAL DOSE						
15 min (± 2 min)	×	×			×	
30 min (± 2 min)	×	×			×	
1 hour (± 3 min)	×	×			×	
1.5 hours (± 3 min)	×	×			×	
2 hours (± 3 min)	×	×			×	
3 hours (± 5 min)	×	×	×[b]		×	
4 hours (± 5 min)	×	×			×	
6 hours (± 10 min)	×	×			×	
8 hours (± 10 min)	×	×			×	
24 hours (± 60 min)[a]	×[a]	×[a]				

[a] The pre-dose time point is the same as the 24-hour time point on the previous day; the 24-hour time point is the same as the pre-dose time point on the following day.

[b] Time-matched PK assessment for QTc on Day 3: ECG is to be done predose and at 3 hr ± 5 min. PK blood draw should be done immediately after completion of ECG for QTc.

NOTE: Volume per blood draw = 3 mL. Total blood volume planned for the ASTX727 cycle = ~99 mL.

NOTE: Every effort should be made to collect PK samples within the specified sampling windows.

Table 7: Schedule of Pharmacokinetics Assessments – IV Decitabine Cycle

		IV Decitabine Cycle					
	Cycle Day	**1**	**2**	**3**	**4**	**5**	**6-28**
Pre-dose (within 90 min before dosing)		×		×[b]		×	
TIME AFTER START OF INFUSION	**TIME AFTER END OF INFUSION**						
15 min (± 2 min)		×				×	
30 min (± 2 min)		×				×	
1 hour (59 min ± 1 min)[a]		×[a]		×[b]		×[a]	
1 hour 5 min (± 1 min)	**5 min** (± 1 min)[c]	×				×	
1.5 hours (± 3 min)	**30 min** (± 3 min)	×				×	
2 hours (± 3 min)	**1 hour** (± 3 min)	×				×	
3 hours (± 5 min)	**2 hours** (± 5 min)	×				×	
4 hours (± 5 min)	**3 hours** (± 5 min)	×				×	
6 hours (± 10 min)	**5 hours** (± 10 min)	×				×	
8 hours (± 10 min)	**7 hours** (± 10 min)	×				×	

[a] Obtain the 1-hour PK sample immediately prior to the end of infusion (59 min ± 1 min).

[b] Time-matched PK assessment for QTc on Day 3: ECG is to be done predose and within 10 min before end of infusion. PK blood draw should be done immediately after completion of ECG for QTc but before the end of the infusion.

[c] The clock for 5 min post-infusion should begin when the infusion is finished.

NOTE: Blood draws for PK should be made from the contralateral arm (arm not used for IV infusion). Volume per blood draw = 3 mL. Total blood volume planned for the IV decitabine cycle = ~72 mL.

NOTE: Every effort should be made to collect PK samples within the specified sampling windows.

9.2 Efficacy Assessments

The response criteria for evaluation of MDS are based on the International Working Group (IWG) criteria published by Cheson et al (2006) modified as shown in Table 8.

Complete response (CR), marrow CR (mCR), partial response (PR), and hematologic improvement (HI) will be determined based on peripheral blood counts and bone marrow aspirate/biopsy at the scheduled assessment days. Red blood cell (RBC) or platelet TI for at least 56 consecutive days will be determined in subjects who are transfusion dependent at baseline of study ASTX727-02. Leukemia free survival is defined as the number of days from the date of randomization to the date when bone marrow or peripheral blood blasts reach ≥20%, or the date of death from any cause. Overall survival is determined from the date of randomization to the date of death from any cause.

Table 8: Response Categories Based on IWG 2006 MDS Response Criteria

Complete Response (CR): the following for at least 4 weeks		
Peripheral: normal peripheral counts with persistent granulocyte count ≥1.0 x 10^9/L, platelet ≥100 x 10^9/L, and Hgb ≥11 g/dL. **Marrow:** normal bone marrow with persistent marrow blasts ≤5%; persistent dysplasia will be noted.		
Partial Response (PR): the following for at least 4 weeks		
Peripheral: normal peripheral counts with granulocyte count ≥1.0 x 10^9/L, platelet count ≥100 x 10^9/L, and Hgb ≥11g/dL. **Marrow:** normal bone marrow and marrow blasts >5% but were reduced by 50% or more.		
Marrow Complete Response (mCR): the following at least for 4 weeks		
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 in the absence of RBC transfusions.
Platelet Response (HI-P):	Major Response:	Absolute increase of platelet count from <20 to >20 X 10^9/L and by at least 100%, or if more than 20 x 10^9/L, by an absolute increase of at least 30 x 10^9/L in the absence of platelet transfusions.
Neutrophil Response (HI-N):	Major Response:	granulocyte increase ≥100%, and by an absolute increase ≥0.5 x 10^9/L.
[a] Abnormal baseline counts should be assessed within one week prior to therapy, not influenced by transfusions (no transfusion for at least 1 week).		

9.3 Pharmacodynamic Assessments

Pharmacodynamic assessments will be based on %LINE-1 demethylation in blood, which will be measured at the following time points:

- Predose on Day 1 of Cycles 1, 2, and 3.
- Days 8, 15, 22 of Cycles 1 and 2.

9.4 Safety Assessments

Safety will be assessed by subject reported and investigator observed AEs, along with physical examination, clinical laboratory tests (hematology, chemistry, urinalysis), ECOG performance status, and electrocardiogram (ECG). Time-matched PK assessments for QTc will be performed at specified time points on Day 3 of Cycles 1 and 2, as described in Table 6.

9.5 Study Procedures

The procedures to be performed in this study are described in detail in this section.

9.5.1 Schedule of Events

Table 9 presents the complete schedule of events for this study, with details following in text. Additional information on the study procedures is provided in the Study Procedures Manual.

Clinical and diagnostic laboratory evaluations are detailed throughout the study. The purpose of obtaining these detailed measurements is to ensure adequate assessments of safety and tolerability. Clinical evaluations and laboratory studies may be performed 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 Institutional Review Board / Independent Ethics Committee (IRB/IEC) according to policy.

Table 9: Schedule of Events

Cycle (28 Days)		1						2						≥3							
Cycle Day		1	2	3	4	5	8, 15, 22	1	2	3	4	5	8, 15, 22	1	2	3	4	5	15	Trtmt Disc.[a]	30-Day F/U
Study treatment administration (Table 5)		×	×	×	×	×		×	×	×	×	×		×	×	×	×	×			
Procedures	**Screening**																				
Informed consent; IPSS risk category, eligibility confirmation	×																				
Medical history	×																				
Randomization	×																				
Physical exam/(symptom-directed PE)[b]	×	(×)						(×)						(×)						×	(×)
Height	×																				
Weight / BSA calculation[c]	×	×						×						×							
Vital signs[d]	×	×	×	×	×	×	×	×	×	×	×	×	×	×						×	
ECOG status[e]	×							×						×						×	×
12-lead ECG[f]	×			×						×											
ECHO or MUGA[g]	×																				
Concomitant treatments/adverse events[h]	×	×	×	×	×	×	×	×	×	×	×	×	×	×						×	×
Transfusion requirements[i]	×	×						×						×						×	×
Pharmacokinetics assessments (Table 6 and Table 7)																					
Laboratory Assessments																					
Hematology[j]	×	(×)					×	×					×	×					×	×	
Chemistry[k]	×							×						×						×	
Urinalysis[l]	×							×						×						×	
Serum or urine pregnancy test[m]	×																			×	
%LINE-1 demethylation (blood)[n]		×					×	×					×	×[n]							
Bone marrow aspirate/biopsy[o]	×													×							

NOTE: Days 8, 15, 22 assessments are permitted within ± 1 day.

[a] Treatment discontinuation: If subject withdraws consent from the study or discontinues treatment, record the reason and complete the indicated procedures. See Section 9.5.6 for following subjects for survival/conversion to AML.

[b] Physical Exam (PE): A complete PE includes examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system and genitourinary system (if applicable). On Cycle 1 Day 1, PE may be symptom-directed if a full PE was completed within 4 days prior.

[c] Weight/BSA calculation: Use actual body weight at Screening for BSA calculation. After Screening, collect body weight only (no BSA needed).

[d] Vital signs: Predose. Assess predose on indicated days, and at treatment discontinuation, after the subject has rested sitting for at least 3 minutes. Include resting systolic/diastolic blood pressure, resting respiration rate, resting heart rate, and body temperature.

[e] ECOG status: Assess at Screening and predose on Day 1 of Cycles ≥2.

[f] 12-Lead ECG (single tracing only, unless clinically significant abnormality for which triplicate ECG is preferred for confirmation, eg, QTc >500 msec). ECG specifically for QTc must be done at Screening and predose on Day 3 of Cycles 1 and 2. Time-matched PK assessment for QTc (Cycles 1 and 2 only): to be done at 3 hr ± 5 min during the ASTX727 cycle, and within 10 min before end of infusion during the IV decitabine cycle (see Table 6 and Table 7, respectively). PK blood draw should be done immediately after completion of ECG for QTc but before the end of the infusion. Either the Bazett's or Fridericia's formula may be used to calculate the QTc interval but must be used consistently throughout the study.

[g] Echocardiogram(ECHO)/ multiple gated acquisition scan (MUGA): May be done within 28 days before first dose of study treatment.

[h] Concomitant treatments/adverse events: Collect concomitant treatments and adverse events at Screening and throughout the study. Include start date when known.

[i] Transfusion requirements: Report transfusions received since previous assessment time point. Final assessment is at the 30-Day Follow-Up Visit.

[j] Hematology: Collect weekly through Cycle 2, at Days 1 and 15 in Cycles ≥3, and at treatment discontinuation. Hematology done during Screening within 1 week before the start of study treatment does not need to be repeated on Cycle 1 Day 1. Complete blood count and differential, with specific output being hemoglobin, platelet count, white blood cell count and percent neutrophils (percent polymorphonuclear neutrophils and bands) or an absolute neutrophil count, and percentage of blasts. Additional laboratory assessments may be done at the investigator's discretion for clinical intervention.

[k] Chemistry: At Screening, predose on Day 1 of Cycles ≥2, and at treatment discontinuation. Must include glucose, calcium, magnesium, albumin, total protein, sodium, potassium, CO_2, chloride, BUN, creatinine, lactate dehydrogenase, alkaline phosphatase, ALT, AST, total bilirubin, direct bilirubin only if total bilirubin is elevated above the protocol inclusion criterion. Additional laboratory assessments may be done at the investigator's discretion for clinical interventions.

[l] Urinalysis: At Screening, predose on Day 1 of Cycles ≥2, and at treatment discontinuation. Dipstick only (microscopic analysis required only to follow up abnormal findings or if dipstick not performed). See Table 10.

[m] Pregnancy test: At Screening and at treatment discontinuation. Serum or urine; only for women of child-bearing potential.

[n] LINE-1 demethylation: Obtain whole blood sample predose on Day 1 of Cycles 1 and 2 (as baseline), Days 8, 15, 22 of Cycles 1 and 2; and Day 1 of Cycle 3.

[o] Bone marrow aspirate or biopsy: At Screening or within 21 days before Cycle 1 Day 1; on or before Day 1 of Cycles 3, 5, 7, and then every 3 months in first year and every 6 months thereafter. Bone marrow aspirate or biopsy differential will be performed according to local standard practice. A bone marrow biopsy can be done if no aspirate is available. A manual differential of the myeloid cells in bone marrow will be performed with a minimum of 100 cells counted and a specific myeloblast percent generated. Bone marrow aspirate or biopsy differential may include the following: total cells counted, metamyelocytes, lymphocytes, normoblasts, myeloid and erythroid maturation, blasts, segmented neutrophils, plasma cells, megakaryocytes, presence of dysplasia, promyelocytes, eosinophils, monocytes, M:E ratio, cellularity: % cellularity; hypocellular, hypercellular, normocellular; myelocytes, basophils, pronormoblasts, and other. An anonymized report of all bone marrow testing results will be recorded on the electronic Case Report Form. A portion of bone marrow aspirates will be used for assessing disease-associated gene mutations. Cytogenetics will be reviewed on the screening bone marrow and should include at least 20 clones. If cytogenetics are abnormal, they must be reviewed again in subsequent bone marrow aspirates or biopsies.

9.5.2 Screening / Baseline Procedures

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

Within 14 days before treatment administration (or as specified below or in Table 9), perform the following study procedures and tests:

- Legally effective informed consent. The ICF must be signed and dated by the subject before any study-specific samples are collected or study-specific procedures are initiated.
- Investigator's confirmation of eligibility. Perform all necessary procedures and evaluations to document that the subject meets each eligibility criterion.
- Assess IPSS and any prior cancer treatments.
- Complete medical history, including demographics. Record disease history, including the date of initial diagnosis. Document concurrent medical signs and symptoms to establish baseline conditions.
- Randomization (confirm with medical monitor): see Section 6.1.
- Complete physical exam (PE) including height and weight, and examination of body systems.
- Obtain height and weight; perform BSA calculation. Use Screening BSA for calculation of IV decitabine dose (for IV decitabine cycle).
- Vital signs include resting systolic/diastolic blood pressure, resting respiration rate, resting heart rate, and body temperature.
- ECOG performance status (see Appendix 1).
- 12-lead ECG: single tracing only unless clinically significant abnormality for which triplicate ECG is preferred for confirmation, eg, QTc >500 msec; rhythm, atrial rate, ventricular rate, PR interval, QRS duration, and QT/QTc, and overall interpretation. Either the Bazett's or Fridericia's formula may be used to calculate the QTc interval but must be used consistently throughout the study.
- ECHO or MUGA: may be performed up to 28 days before study treatment.
- Record concomitant medications.
- Transfusion requirements: record transfusions received since previous assessment time point: up to 56 days prior if data are available.
- Collect blood samples for hematology and serum chemistry, and urine sample for urinalysis.
- 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.

- Collect bone marrow aspirate or biopsy (must be collected within 21 days before first dose of study treatment).

Table 10: Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis	Pregnancy Test
-Complete blood count (CBC) and differential (hemoglobin, platelet count, white blood cell count and percent neutrophils (percent polymorphonuclear neutrophils and bands) or an absolute neutrophil count, and percentage of blasts)	-Glucose -Calcium -Magnesium -Albumin -Total protein -Sodium -Potassium -CO_2 -Chloride -BUN -Creatinine -Lactate dehydrogenase -Alkaline phosphatase -ALT -AST -Total bilirubin -Direct bilirubin (only if total bilirubin is elevated)	-Dipstick only (microscopic analysis required only to follow up abnormal findings or if dipstick not performed) -Specific gravity -pH -Protein -Glucose -Ketones -Leukocyte esterase -Blood -Microscopic urinalysis -Color -Clarity	-Urine or serum

Note: The frequency of these assessments is given in Table 9.

9.5.3 Treatment Procedures

9.5.3.1 Cycle 1 – Day 1

- Perform the following procedures before administration of study treatment:
  - Complete PE (may be a symptom-directed PE if a full PE was completed within 4 days of this visit).
  - Body weight.
  - Vital signs.
  - Record concomitant medications and adverse events.
  - Record transfusion requirements.
  - Collect blood samples for hematology. NOTE: hematology done during Screening within 1 week before the start of study treatment does not need to be repeated on Cycle 1 Day 1.
  - Obtain whole blood sample for %LINE-1 demethylation.
  - Pharmacokinetics assessment.
- Perform the following procedures at the specified time points:
  - Pharmacokinetics assessments.

9.5.3.2 Cycle 1 – Day 2 through Day 4

- Perform the following procedures before administration of study treatment:
  - Vital signs.
  - ECG including QTc interval – Day 3 only.
  - Record concomitant medications and adverse events.
  - Pharmacokinetics assessment – only Day 3 during IV decitabine cycle.
- Perform the following procedures at the specified time points:
  - Pharmacokinetics assessments: Day 2 (if ASTX727 given this cycle), and Day 3.
  - ECG with QTc interval on Day 3 as specified in Table 6 or Table 7, depending upon treatment cycle.

9.5.3.3 Cycle 1 – Day 5

- Perform the following procedures before administration of study treatment:
  - Vital signs.
  - Record concomitant medications and adverse events.
  - Pharmacokinetics assessments.
- Perform the following procedures at the specified time points:
  - Pharmacokinetics assessments.

9.5.3.4 Cycle 1 – Days 8, 15, 22

- Assessments are permitted within ± 1 day:
  - Vital signs.
  - Record concomitant medications and adverse events.
  - Collect blood samples for hematology.
  - Obtain whole blood sample for %LINE-1 demethylation assessment.

9.5.3.5 Cycle 2 – Day 1

- Perform the following procedures before administration of study treatment:
  - Complete PE including weight/BSA (may be a symptom-directed PE).
  - Body weight.
  - Vital signs.
  - ECOG performance status (Appendix 1).

- 12-lead ECG: single tracing only.
- Record concomitant medications and adverse events.
- Record transfusion requirements.
- Collect blood samples for hematology and chemistry, and perform urinalysis.
- Obtain whole blood sample for %LINE-1 demethylation assessment.

- Pharmacokinetics assessments.

9.5.3.6 Cycle 2 – Day 2 through Day 4

- Perform the following procedures before administration of study treatment:
  - Vital signs.
  - ECG including QTc interval – Day 3 only.
  - Record concomitant medications and adverse events.
  - Pharmacokinetics assessment – only Day 3 during IV decitabine cycle.
- Perform the following procedures at the specified time points:
  - Pharmacokinetics assessments: Day 2 (only if ASTX727 given this cycle), and Day 3.
  - ECG with QTc interval as specified in Table 6 or Table 7, depending upon treatment cycle.

9.5.3.7 Cycle 2 – Day 5

- Perform the following procedures before administration of study treatment:
  - Vital signs.
  - Record concomitant medications and adverse events.
- Pharmacokinetics assessments.

9.5.3.8 Cycle 2 – Days 8, 15, 22

- Assessments are permitted within ± 1 day:
  - Vital signs.
  - Record concomitant medications and adverse events.
  - Collect blood samples for hematology.
  - Obtain whole blood sample for %LINE-1 demethylation assessment.

9.5.3.9 Cycles ≥3 – Day 1

- Perform the following procedures before administration of study treatment:
  - Complete PE including weight (may be a symptom-directed PE).
  - Body weight.
  - Vital signs.
  - ECOG performance status (Appendix 1).
  - Record concomitant medications and adverse events.
  - Record transfusion requirements.
  - Collect blood samples for hematology and chemistry, and perform urinalysis.
  - Obtain whole blood sample for %LINE-1 demethylation assessment (Cycle 3 only).
  - Collect bone marrow aspirate or biopsy.

9.5.3.10 Cycles ≥3 – Day 15

- Collect blood samples for hematology.

9.5.4 Treatment Discontinuation

Confer with the Astex medical monitor before discontinuing treatment for a given subject.

If the subject withdraws consent from the study or is discontinued from study treatment at any time before finishing Cycles 1 and 2, complete the following procedures:

- Complete PE.
- Vital signs.
- ECOG performance status (Appendix 1).
- Record concomitant medications and adverse events.
- Record transfusion requirements.
- Record the specific reason the subject terminated treatment.
- Collect blood samples for hematology and serum chemistry, and urine sample for urinalysis.
- Serum or urine pregnancy test: for women of child-bearing potential only.

9.5.5 30-Day Follow Up

The 30-Day Follow-up Visit must occur 30 (+5) days after the last dose of study treatment or within 3 days before starting new anti-cancer treatment (do not record medications taken during new treatment), whichever is sooner. This visit may be conducted in person or by telephone. For

30-Day Follow-up via telephone, assess as much as possible but at a minimum assess AEs. Also record any new therapy for the subject's disease.

- Symptom-directed PE.
- ECOG performance status (Appendix 1).
- Record concomitant medications and adverse events.
- Record transfusion requirements.

9.5.6 Survival/Conversion to AML

Follow all subjects for survival/conversion to AML who have stopped study treatment. Contact subject every 3 months until death or withdrawal of consent or the close of the trial. This assessment may be conducted by telephone.

9.6 Missed Evaluations

Evaluations should occur within the visit window specified by the protocol, as applicable. 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.

10.0 EVALUATION, RECORDING, AND REPORTING OF ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Event

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

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 any AEs related to screening procedures that occur before the start of study treatment.

Record new AEs from the start of study treatment to the earliest of the following, as applicable:

- Until 30 days after the last dose of study treatment, or
- Until the subject starts new MDS/CMML treatment, including new investigational treatment.

Record in the eCRF all AEs from any source (eg observed by study personnel, reported by the subject, or from the subject's medical record). 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 v4.03 (Appendix 2) for grading the severity (intensity) of AEs. The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE and provides guidance not listed. Should a subject experience any AE not listed in the CTCAE v4.03, use the following grading system to assess severity:

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

10.2.2 Relationship to Study Treatment (Suspected Adverse Reactions)

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

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

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

Related (Suspected Adverse Reaction)	A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE such as a plausible temporal relationship between the onset of the AE and administration of the drug; and/or the AE follows a known pattern of response to the drug; and/or the AE abates or resolves upon discontinuation of the drug or

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

10.2.3 Pregnancy and Abortion

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

A subject must immediately inform the investigator if the subject or subject's partner becomes pregnant during the time between the first study-specific procedure and 60 days after the last dose of study treatment. Any female subjects receiving ASTX727 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 Clinical Safety and Risk Management 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 Clinical Safety and Risk Management (or via a designee) 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.

Enter all SAEs (initial and follow-up information) into the electronic data capture (EDC) database within 24 hours of awareness. The EDC system will automatically send the SAE report via the Safety Gateway to Astex Pharmaceuticals Clinical Safety and Risk Management. Astex Pharmaceuticals may request follow-up and other additional information from the investigator (eg, hospital admission or discharge notes, laboratory results). Additional source documents can be emailed to the address below. If the EDC system is not accessible for any reason, the SAE form will need to be completed and sent to Astex Pharmaceuticals Clinical Safety and Risk Management. When the EDC system becomes available, the information on the SAE form shall be entered into EDC.

Astex Pharmaceuticals Clinical Safety and Risk Management Contact Information	
Primary Contact Email	DrugSafety@astx.com

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 Clinical Safety and Risk Management, 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 Clinical Safety and Risk Management 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 9.4 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, 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

A preliminary analysis of 5-day AUC in study ASTX727-01 shows an estimate of intra-subject CV of 0.5. A conservative CV value of 0.55 was chosen to calculate the sample size.

A total of 118 subjects in the Primary Endpoint PK Analysis Set (Section 11.2.2) included in the 2 one-sided equivalence tests for the geometric mean ratio of ASTX727 5-day AUC relative to IV decitabine 5-day AUC will provide 90% power at the statistical significance level of 0.05, when the true ratio of geometric means is 1.0, the CV under an unlogged scale is 0.55, and the 90% CI equivalence limits for the ratio of geometric means are 0.8 and 1.25. Assuming 10% of subjects may not be evaluable in the study, approximately 132 subjects will need to be randomized.

11.2 Analysis Sets to be Analyzed

11.2.1 All Subject Analysis Set

The **All Subject Analysis Set** will include information from all screened subjects, including those who did not meet the study entry criteria or who did not receive a study treatment. This data set will be used only for disposition in which all screened subjects are accounted.

11.2.2 Pharmacokinetics Analysis Sets

Two PK analysis sets will be used for analysis of PK data, as described below.

The **Primary Endpoint PK Analysis Set** will be used for calculating decitabine 5-day AUC_{0-t} and bioequivalence statistical analysis. This analysis set will include decitabine daily AUC_{0-t} from subjects who are successfully dosed in Cycles 1 and 2 (see below) and who meet the following criteria for both ASTX727 and IV decitabine dosing.

ASTX727 successful dosing: received full dose of ASTX727 within 3 hours of the intended dosing time, and no vomiting within 6 hours of dosing.

- Subjects in this analysis set will have at least 2 days of evaluable decitabine AUC_{0-t} measurements in the ASTX727 cycle, ie, Day 1 and either Day 2 or Day 5:

- For Day 1 to be included, subjects must have been successfully dosed on Day 1.
- For Day 2 to be included: subjects must have been successfully dosed on Day 1 and Day 2.
- For Day 5 to be included: subjects must have been successfully dosed on Day 4 and Day 5.

IV decitabine successful dosing: received the full dose as a 1-hour infusion.

- Subjects in this analysis set will have at least 1 evaluable day of decitabine AUC_{0-t} measurement in the IV decitabine cycle, either Day 1 or Day 5.

The **Overall PK Analysis Set** will be used for calculating PK parameters, including decitabine daily AUC_{0-t}, which will be used to derive the primary PK endpoint of decitabine cumulative 5-day AUC_{0-t} exposures, and other secondary PK parameters for decitabine, cedazuridine, and cedazuridine-epimer. This analysis set will include subjects who may or may not be included in the Primary PK Analysis set and who meet the following criteria:

- Received any amount of study treatment.
- Complied with the protocol sufficiently to ensure PK samples were collected as intended.
- Provided sufficient samples to measure available plasma concentrations for decitabine, cedazuridine, and cedazuridine-epimer.

11.2.3 Efficacy Analysis Set

The Efficacy Analysis Set will include data from all subjects who received at least one full dose (day) of study treatment. 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.

11.2.4 Safety Analysis Set

The Safety Analysis Set will include all subjects who received any amount of study treatment. All data will be included, and no subjects will be excluded because of protocol violations.

11.2.5 Pharmacodynamics Analysis Set

Subjects will be included in the PD Analysis Set if they have received at least one dose of study treatment and have %LINE-1 methylation data at baseline (Day 1) of Cycle 1 or 2 and on either Day 8 or Day 15 of the respective cycle.

11.3 Schedule of Analyses

Pharmacokinetics for the primary study endpoint, PD, and safety analyses will be performed after all evaluable subjects have completed Cycles 1 and 2. Additional secondary endpoint analyses will be performed after all subjects discontinue treatment or complete at least 6 cycles of treatment.

11.4 Subject Disposition

The number and percentage (n, %) of subjects enrolled, treated, lost to follow up, and withdrawn (with reason) will be summarized. Sample size for the Efficacy Analysis Set, Safety Analysis Set, PK Analysis Set, and PD Analysis Set will be clearly identified for each treatment sequence. All subjects in the All Subject Analysis Set 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 (SD), median, minimum, and maximum for continuous variables; and by counts and percentages for categorical variables. Summaries will be provided separately for each treatment sequence and both sequences combined. The Efficacy Analysis Set will be used for the summaries.

11.6 Pharmacokinetics Analyses

A detailed description of the PK analyses is in the Pharmacokinetic Analysis Plan. A brief description follows below.

11.6.1 Primary Pharmacokinetics Endpoint Analyses

The primary PK endpoint analyses will be performed in the order presented below.

Calculation of daily decitabine AUC_{0-t}

The Overall PK Analysis Set will be used for calculation of decitabine AUC_{0-t}. Decitabine AUC_{0-t} by Cycle and Day will be calculated by the linear up/log down non-compartmental method using the measured concentration-time values above the quantitation limit using Phoenix® WinNonlin.

In the case of a missed sample collection, enough data should be available for reliable calculation of the parameter AUC_{0-t}. To be considered reliable for calculation of AUC_{0-t} without imputation of missing data, a plasma PK profile should contain more than 5 consecutive data points with a quantifiable concentration value, including at least 3 data points beyond the T_{max}, and $\%AUC_{extrap}$ ((1－[AUC0-t/AUC0-inf])×100) should not exceed 20% for each individual profile.

Individual values of decitabine daily AUC_{0-t} will be used for generating the Primary Endpoint PK Analysis Set from evaluable subjects as described above. A listing of individual values of decitabine daily AUC_{0-t} Cycle and Day, and non-model-based descriptive statistics will be provided. However, decitabine daily AUC_{0-t} from subjects who are not evaluable to be included in the Primary Endpoint PK Analysis Set will be identified in the listing but will not be included in descriptive statistics; the reason for exclusion will be provided.

Calculation of decitabine 5-day AUC_{0-t}

The Primary Endpoint PK Analysis Set will be used to calculate decitabine 5-day cumulative AUC_{0-t} exposures after ASTX727 treatment. The following assumptions will be used:

- Steady state is reached on Day 2 of dosing with ASTX727.
- Based on steady state achievement on Day 2, decitabine AUC_{0-t} from Day 2 and Day 5 would be representative of daily AUC_{0-t} on Days 2 through Day 5 in a putative 5-day dosing with ASTX727.

Therefore, to calculate total 5-day oral decitabine AUC_{0-t} exposures using PK data from 3 days sequential PK sampling, Day 1 AUC_{0-t} (first ASTX727 dose) will be added to (Day 2 AUC_{0-t} + Day 5 AUC_{0-t}) × 2. If AUC_{0-t} on Day 2 is not available, it will be replaced by AUC_{0-t} on Day 5; the converse is also true.

To calculate decitabine 5-day AUC_{0-t} exposures after IV decitabine, (Day 1 AUC_{0-t} + Day 5 AUC_{0-t}) / 2 will be multiplied by 5, based on Dacogen prescribing information (current Dacogen Prescribing Information) that there was no accumulation on Day 5 vs Day 1 for a 5-day infusion. If AUC_{0-t} on Day 1 is not available, it will be replaced by AUC_{0-t} on Day 5; the converse is also true.

Bioequivalence statistical analysis of decitabine 5-day AUC_{0-t} between ASTX727 and IV decitabine treatments

Decitabine AUC_{0-t} equivalence analysis will be performed on the Primary Endpoint PK Analysis Set.

The primary endpoint, decitabine 5-day AUC_{0-t}, will be analyzed in the log scale using a mixed effect model including fixed effects of sequence, period, and treatment, and a random effect of subject within sequence (EMA 2010; EMA 2015). The factors to be included in the model will be based on the actual treatment sequence. A 90% CI for the geometric mean ratio of 5-day AUC_{0-t} will be obtained by applying the exponential function on the 2-sided 90% CI for the difference of mean 5-day AUC_{0-t} between ASTX727 and IV decitabine in the log scale from the mixed effect model. The decitabine AUC_{0-t} equivalence will be established if the 90% CI for the geometric mean ratio is contained within the interval (0.8, 1.25).

11.6.2 Other Pharmacokinetics Variables

Calculation of other secondary PK parameters will be performed on the Overall PK Analysis Set. Pharmacokinetics parameters will be calculated by noncompartmental analysis methods from the concentration-time data using Phoenix® WinNonlin®.

Decitabine PK parameters AUC_{0-inf}, C_{max}, T_{max}, clearance (CL/F), apparent volume of distribution (Vd/F), and apparent half life ($t_{1/2}$) are of secondary interest and will be reported together with AUC_{0-t} where applicable. The PK parameters of cedazuridine and cedazuridine-epimer will be also reported.

Individual values will be listed for each PK parameter by treatment and analyte, and the following (non-model-based) descriptive statistics will be provided: number of subjects with non-missing

data, arithmetic mean, standard deviation, arithmetic percent, median, minimum, maximum, geometric mean, and geometric percent CV. Note that CL/F and Vd/F will be calculated only for decitabine and cedazuridine and will not be calculated for cedazuridine-epimer.

A population PK analysis for evaluation of various covariates and exposure-response will also be performed.

11.7 Efficacy Analyses

Unless otherwise specified, the Efficacy Analysis Set will be used for all efficacy analyses. Efficacy endpoints will be analyzed as one treatment group regardless of randomization.

11.7.1 Clinical Response

Complete response, mCR, PR, and HI (also HI-E, HI-P, and HI-N separately) will be summarized for all subjects in the Efficacy Analysis Set. The rate of each response status and its 95% Wald CIs will be provided, respectively.

11.7.2 Transfusion Independence

Transfusion independence (TI) will be analyzed separately for platelet and RBC TI, the latter defined as no RBC transfusion for 56 consecutive days while maintaining hemoglobin ≥8 g/dL. Platelet TI is defined as no platelet transfusion for 8 consecutive weeks, while maintaining platelets $\geq 20 \times 10^9$/L. Transfusion independence rates will be calculated based on subjects who are in the Efficacy Analysis Set and who were transfusion dependent at baseline. The 95% Wald CIs will be provided separately for the RBC and platelet TI rates.

11.7.3 Leukemia-Free Survival

The number of days from randomization to the date when bone marrow or peripheral blood blasts reach ≥20%, or death from any cause, will be measured for subjects in the Efficacy Analysis Set. Subjects who do not have events in leukemia-free survival will be censored on the last date of bone marrow or peripheral blood blasts assessment, whichever is later. Subjects who have bone marrow or peripheral blood blasts ≥20% at baseline will be censored at the date of randomization. Leukemia-free survival will be presented using a Kaplan-Meier estimate. The 95% CI for the median of leukemia-free survival will be provided using the Kaplan-Meier procedure.

11.7.4 Overall Survival

Overall survival 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 they were known to be alive. Overall survival will be presented using a Kaplan-Meier estimate. The 95% CI for median OS will be provided using the Kaplan-Meier procedure.

11.8 Safety Analyses

The Safety Analysis Set will be used for all safety analyses. Safety will be assessed by subject reported and investigator observed AEs, along with concomitant medications, physical examination, clinical laboratory tests (hematology and serum chemistry), vital signs, ECOG performance status and ECG. Safety will also be assessed by exposure to ASTX727 or IV decitabine, 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 (Appendix 2). All AEs collected during the study will be presented in data listings. Treatment-emergent AEs (TEAEs) are defined as events that first occur or worsen after the subject receives study drug on C1D1 until 30 days after the last dose of study treatment, or the start of an alternative anti-cancer treatment for MDS/CMML or subsequent leukemia, whichever occurs first, 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 based on the treatment period when the events occur:

- 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 will be graded, if possible, by CTCAE in conjunction with the Harrison (18th edition) laboratory normal reference ranges. 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 (Anatomical Therapeutic Chemical [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.

11.9 Pharmacodynamics Analyses

Subjects in the PD Analysis Set will be included in the PD analyses. To avoid the confounding effects of differing baselines in Cycle 2 vs Cycle 1 observed in study ASTX727-01, subjects will be compared for each of the 2 cycles separately, thus limiting the evaluation to interpatient comparisons in each of the 2 cycles.

The 95% CI for the difference of mean maximum %LINE-1 demethylation between ASTX727 and IV decitabine in Cycles 1 and 2 will be generated using an analysis of variance (ANOVA) model. The 95% CIs for mean maximum %LINE-1 demethylation will also be generated for ASTX727 and IV decitabine, respectively. Descriptive statistics including arithmetic mean, SD, median, and range will be summarized by visit and actual treatment. Descriptive statistics for maximum %LINE-1 demethylation will also be summarized by actual treatment.

11.10 Interim Analysis

No interim analysis is planned for this study.

11.11 Procedures for Handling Missing, Unused, and Spurious Data

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

12.0 STUDY DURATION AND TERMINATION

The expected study duration is approximately 18 months (12 months enrollment and at least 6 months of treatment and follow up) and is expected to start in late 2017 or early 2018.

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 must provide legally effective informed consent.

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, any protocol amendments, and the informed consent form (ICF) for the proposed study, along with any other required documents to the study 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 following materials to each study center:

- Initial supply of ASTX727 tablets.
- IV decitabine to study centers outside the US (Section 14.2.2).
- IB for ASTX727.
- Approved labeling for Dacogen.
- eCRFs and other data collection tools as applicable.

Refer to the ASTX727-02 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 ASTX727 and are unexpected (see Section 10.1.2), as appropriate. The investigator must forward this documentation to the IRB/IEC, as described in Section 10.2.

The sponsor will also notify the investigator about any other significant safety findings that could alter the safety profile of ASTX727 from that 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 SSC (Section 4.4) such as limiting the eligibility criteria or reducing the ASTX727 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 drugs are stored properly and under the proper conditions, that they are in sufficient supply, and that receipt, use, and return of study drug 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 randomized or treated.

14.2.2 Study Treatment Accountability

An initial supply of ASTX727 tablets will be provided to all study centers, and resupplies will be handled through an automated inventory management system. Study centers in the US are expected to supply commercially available IV decitabine. Astex will supply IV decitabine to study centers in territories where it is not approved for use.

Keep study treatments in a locked, limited-access room. The study treatments must not be used outside the context of the protocol. Under no circumstances should the investigator or other study center personnel supply the study treatments 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 ASTX727 and decitabine 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 study treatments and other study material are destroyed or returned to the sponsor on completion of the study. If the study treatments are destroyed at the study center, there should be documentation of destruction at the study center. The sponsor and/or representatives will verify final drug accountability. 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.

14.2.5 Tissue and Blood Sample Collection/Storage

Tissue and blood samples collected as part of routine medical care or as part of protocol procedures may be stored and analyzed for pharmacokinetic or pharmacodynamic analyses.

After the study, samples may be used for additional investigation to help identify factors that may influence response to therapy. Such samples will be used in compliance with guidelines defined by FDA Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable (issued 25 April 2006) and European Agency for the Evaluation of Medicinal Products (EMEA) Reflection Paper on Pharmacogenomic Samples, Testing and Data Handling (EMEA 2007).

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 SSC 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. 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.

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17.0 APPENDICES

APPENDIX 1: ECOG AND KARNOFSKY PERFORMANCE STATUS

Score	ECOG Description	Score	Karnofsky Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints.
		90	Able to carry on normal activities; minor signs or symptoms of disease.
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.	80	Normal activity with effort.
		70	Care for self. Unable to carry on normal activity or do active 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.	60	Requires occasional assistance; cares for most needs.
		50	Requires considerable assistance and frequent medical care.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled: requires special care and assistance.
		30	Severely disabled: hospitalization indicated though death not imminent.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick: hospitalization necessary. Active support treatment necessary.
		10	Moribund.
5	Dead.	0	Dead.

Sources:

ECOG Performance Status — http://www.ecog.org/general/perf_stat.html (accessed 29 August 2017).

Karnofsky Performance Status — http://oncologypro.esmo.org/Guidelines-Practice/Practice-Tools/Performance-Scales (accessed 29 August 2017).

APPENDIX 2: COMMON TERMINOLOGY FOR ADVERSE EVENTS V4.0 (CTCAE V4.03)

For the NCI-CTCAE version 4.03, refer to the following:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf (accessed 05 December 2020)

APPENDIX 3: MODIFICATIONS DURING THE COVID-19 HEALTH EMERGENCY

General Information

This section describes modifications to the study protocol which will be implemented to allow flexibility in conducting this study during the current COVID-19 public health emergency or re-emergence of the same, while maintaining safety of trial subjects, maintaining compliance with GCP, and minimizing risks to trial integrity. These modifications are intended to remain in effect **only** for the duration of the public health emergency related to COVID-19 and only in instances where the study cannot be conducted per the protocol.

Any modifications to the study protocol must be discussed with the Astex medical monitor before implementing.

Study Status

In extenuating circumstances (eg, during the COVID-19 pandemic), Astex may implement all or some of the following modifications:

- Temporarily pause recruitment of new trial subjects.
- Extend the duration of the study.
- Postpone activation of study centers that have not been initiated.
- Transfer of study subjects to investigational study centers away from high-risk zones or closer to their home.
- Conversion of physical visits to telephone or video visits.
- Modification to ensure that only strictly necessary visits are performed at study centers.
- Allow laboratory test and/or diagnostic tests to be conducted at a local laboratory/facility authorized/certified to perform such tests.
- Remote monitoring source data review/verification, where permitted by regulations.
- Changes to the per-protocol informed consent process in accordance with IRB/IEC and Institutional guidelines.

COVID-19 Benefit/Risk Assessment

The safety of each trial subject is of primary importance. Astex will continually reassess the risks of conducting this clinical trial against the anticipated benefit for trial subjects as the COVID-19 situation evolves and implement and document changes accordingly.

It is possible that local circumstances may lead to a local change in risk assessment (eg, an escalation of the pandemic within a certain region); therefore, the need to implement additional

measures may arise. Investigators may be asked to complete a risk assessment questionnaire provided by Astex. This assessment should be documented in the investigator's site master file and communicated to Astex.

Modifications to Study Conduct

Alternative Methods for Obtaining Informed Consent

Alternative methods for obtaining informed consent may be used for re-consenting subjects if necessary and must be appropriately documented in each subject's chart. Alternative methods include but are not limited to contacting the trial subject via telephone or video-calls and obtaining oral consent, supplemented with e-mail confirmation, etc, as per IRB/IEC and Institutional policies or guidelines.

Alternative Methods for IMP Shipment

In extenuating circumstances (eg, during the COVID-19 pandemic) where standard approaches to dispensing study drug to subjects are not possible, alternative methods for dispensing study drug to subjects may be used. Astex will work with individual sites to find acceptable alternative arrangements (eg, shipment of study drug from study center pharmacies to subjects) that assure compliant control of study drug and acceptable safety monitoring. Alternative methods for drug dispensing must be reviewed by Astex before implementing.

Study Visits and Procedures

Protocol-mandated visits and laboratory/diagnostic testing may be modified as follows (and documented as protocol deviations):

- Study subjects may use local laboratories for standard laboratory testing (eg, hematology, serum/plasma chemistry, and urinalysis)
- Telemedicine visits (ie, conducted via telephone and/or video calls, or in-person Telehealth Visits with a health professional) may be permitted in lieu of in-person visits to monitor AEs and subject safety.
- Telemedicine visits must be approved by Astex and aligned with institutional practice and local regulations.
- Telemedicine visits must be appropriately documented in source documents.
- Additional details regarding how to conduct telemedicine visits will be provided by Astex.

In-person visits are required to assess eligibility, perform baseline assessments, and for primary outcome measures. Telemedicine visits would generally not be permitted for the following procedures unless approved by Astex:

- Screening and/or pre-dose Cycle 1 Day 1 assessments to determine eligibility.

- Visits with blood sample collection for PK analysis.
- Bone marrow collection.
- Day 1 cycle visits when a subject is in early cycles of the protocol-defined treatment.

APPENDIX 4: SUMMARY OF CHANGES

Rationale for Amendment 2.0

Amendment 2 is a global amendment that is being applied to the original protocol. Due to later amendments to generate regional protocols, Amendment 2.0 is now the US protocol.

Summary of Changes:

Minor edits to the text for clarity are not included below, but are provided in the redline version of the protocol (provided as a separate document).

1. Addition of information on marketing approval of ASTX727 as INQOVI® (35 mg decitabine/100 mg cedazuridine) (Synopsis, Section 1.3, and Section 7.1).
2. Addition of language describing modifications to study conduct implemented due to the current COVID-19 health emergency (Section 4.1 and Appendix 3).
3. Removal of restriction on ingestion of medication that may affect gastric pH for 4 hours before and 4 hours after ASTX727 dosing because PK results have shown this is not required (Synopsis, Section 7.4, and Section 7.7.2).
4. Description of informed consent is changed from "written informed consent" to "legally effective informed consent" (Synopsis, Section 5.2, Section 6.0, Section 9.5.2, and Section 13.2).
5. Further details and guidance on antibiotic prophylaxis are provided at the request of a health authority (Section 7.7.1).
6. Exclusion criterion for "Hypersensitivity to decitabine, cedazuridine, or any of the excipients in ASTX727 tablets or IV decitabine" is added at the request of a health authority (Synopsis and Section 5.3).
7. A brief summary of PK results from the MDS subjects in this study is added at the request of a health authority (Section 1.4.3).
8. A paragraph emphasizing the importance of multiple cycles of treatment after completion of Cycles 1 and 2 is added at the request of a health authority (Section 4.1).
9. An explanation that assessment of efficacy and safety is independent of the PK endpoints is added at the request of a health authority (Section 4.2).
10. Instructions regarding what to do in the event of a vomited dose are added at request of a health authority (Section 7.5.2).
11. Instructions that dosing should be delayed in presence of certain non-hematologic toxicities are added at the request of a health authority (Section 7.6).

12. Prohibition of nucleosides or drugs metabolized by CDA is extended from days that ASTX727 is administered to entire duration of study treatment at the request of a health authority, and a non-inclusive list of such drugs is (Section 7.7.2).
13. ASTX727 is identified as genotoxic, based on the current INQOVI Prescribing Information (Section 8.2).
14. Description of AE reporting is updated to align with current practice (Section 10.2).
15. SAE reporting requirements are updated to align with current practice that includes automated sending of SAE reports through the Safety Gateway (Section 10.3).
16. Administrative changes including a name change for Astex Drug Safety to “Astex Clinical Safety and Risk Management”, reference to current labelling information, updating hyperlinks, and addition of references as applicable.