Clinical Study Protocol — ASTX727-01

NCT02103478

A Phase 1-2 Pharmacokinetic Guided Dose-Escalation and Dose-Confirmation Study of ASTX727, a Combination of the Oral Cytidine Deaminase Inhibitor (CDAi) E7727 with Oral Decitabine in Subjects with Myelodysplastic Syndromes (MDS)

PROTOCOL TITLE PAGE

Sponsor:	Astex Pharmaceuticals, Inc. 4420 Rosewood Dr., Suite 200 Pleasanton, CA 94588
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Study Acknowledgement

A Phase1-2 Pharmacokinetic Guided Dose-Escalation and Dose-Confirmation Study of ASTX727, a Combination of the Oral Cytidine Deaminase Inhibitor (CDAi) E7727 with Oral Decitabine in Subjects with Myelodysplastic Syndromes (MDS)

Version 5.0: Amendment 4 (06 April 2017)

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

[redacted]

INVESTIGATOR STATEMENT

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

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

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

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

PROTOCOL APPROVAL PAGE

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Version 5.0: Amendment 4 (06 April 2017)

AUTHORS

PROTOCOL APPROVAL PAGE

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Version 5.0: Amendment 4 (06 April 2017)

QA APPROVAL

[redacted]

APPROVED BY

[redacted]

PROTOCOL SYNOPSIS

Study Number and Title:

ASTX727-01: A Phase 1-2 Pharmacokinetic Guided Dose-Escalation and Dose-Confirmation Study of ASTX727, a Combination of the Oral Cytidine Deaminase Inhibitor (CDAi) E7727 with Oral Decitabine in Subjects with Myelodysplastic Syndromes (MDS)

Investigational Medicinal Product:

E7727 oral: 20 mg hard gelatin white opaque capsules

Decitabine oral: 20 mg hard gelatin Swedish orange capsules; 5 mg hard gelatin light blue capsules

The fixed-dose combination (FDC) drug form of ASTX727 is a film-coated, oval, white, immediate-release tablet containing the combination of E7727 (100 mg) and decitabine (35 mg) for oral administration.

Clinical Phase: 1-2

Study Centers Planned/Country: Multicenter: United States, Canada

Study Objectives:

Dose Escalation Stage

Primary Objectives

- Assess safety, tolerability, and pharmacokinetics (PK) of concomitant orally administered decitabine + E7727.
- Identify a dose of oral decitabine + E7727 that together achieve a target mean decitabine AUC comparable to that from decitabine given by IV infusion (20 mg/m^2) for 1 hour.

Secondary Objectives

- Determine percent change of LINE-1 demethylation in Course 1 and Course 2.
- Assess preliminary efficacy, as determined by response rate, duration of response, hematological improvement, rate of transfusion independence, time to AML, and overall survival.
- Evaluate other PK parameters of decitabine, E7727, and E7727-epimer.

Exploratory Objectives

[redacted]

Dose Confirmation Stage

Primary Objectives

- Confirm the dose of oral decitabine + E7727 identified in the Dose Escalation Stage administered daily×5 that achieves mean decitabine AUC (estimated from 5 days of dosing) and LINE-1 DNA demethylation comparable to that of IV decitabine 20 mg/m^2 daily×5.
- Assess response rate in all subjects.

Secondary Objectives

- Assess safety and tolerability of oral decitabine + E7727.
- Assess duration of response, hematological improvement, rate of transfusion independence, time to AML, and overall survival.
- Evaluate other PK parameters of oral decitabine, E7727, and E7727-epimer (if needed).

Exploratory Objective

[redacted]

Fixed-Dose Combination Stage

Primary Objectives

- Confirm the ASTX727 FDC tablet achieves mean decitabine AUC (estimated from 5 days of dosing) and LINE-1 DNA demethylation similar to that for IV decitabine 20 mg/m^2 daily×5.
- Assess response rate in all subjects.

Secondary Objectives

- Assess safety and tolerability of ASTX727.
- Assess duration of response, hematological improvement, rate of transfusion independence, time to AML, and overall survival.

- Evaluate other PK parameters of ASTX727.

Exploratory Objective

[redacted]

Study Design and Investigational Plan:

Study ASTX727-01 will consist of 3 stages: a Dose Escalation Stage, a Dose Confirmation Stage, and a Fixed-Dose Combination Stage.

Dose Escalation Stage

The Dose Escalation Stage is a single-arm PK-guided 3+3 dose escalation study in subjects with intermediate- or high-risk MDS who are candidates for treatment with a hypomethylating agent. At least 3 evaluable subjects will be enrolled in each cohort.

Dosing:

Course 1:

- Day -3 (±2 days): Single dose oral decitabine.
- Day 1: Decitabine by 1-hour IV infusion administered at 20 mg/m^2.
- Days 2-5: Concomitant oral administration of decitabine + E7727.

Course 2:

- Day -3 (± 2 days): Single dose E7727.
- Days 1-5: Concomitant oral administration of decitabine + E7727.

Course ≥3:

- Days 1-5: Concomitant oral administration of decitabine + E7727.

All subjects will continue to receive oral decitabine + E7727 daily×5 of a 28-day course in Course 3 and thereafter until the subject has disease progression or unacceptable toxicity, or the subject withdraws consent or is withdrawn from the study.

If no dose limiting toxicities (DLTs) occur in cohort 1 during Course 1, E7727 or oral decitabine will be escalated/de-escalated in subsequent cohorts according to protocol Section 4.1.1 until the target mean AUC for oral decitabine approaches as close to unity with IV decitabine 20 mg/m^2 as possible.

For the protection of study subjects, a Data and Safety Review Committee (DSRC) will review and evaluate at least the 28-day Course 1 safety and PK data from a minimum of 3 evaluable subjects at each dose cohort, and will agree on the dose level of oral decitabine and E7727 for the next cohort or agree to expand the current cohort (Section 4.4).

Dose Confirmation Stage

The Dose Confirmation Stage is a randomized comparison between oral decitabine + E7727 at the doses established in the Dose Escalation Stage and IV decitabine 20 mg/m^2 1-hour infusion both given daily for 5 days in at least 42 evaluable subjects. Subjects will be randomized to the sequence of

- Oral decitabine + E7727 daily×5 in Course 1 followed by IV decitabine daily×5 in Course 2, or
- IV decitabine daily×5 in Course 1 followed by oral decitabine + E7727 daily×5 in Course 2.

Beginning with Course 3 and all subsequent courses, subjects will receive oral decitabine + E7727 daily×5 of a 28-day course until the subject has disease progression or unacceptable toxicity, or the subject withdraws consent or is withdrawn from the study.

Fixed-Dose Combination Stage

This stage is a comparison between a fixed-dose tablet form of ASTX727 and IV decitabine 20 mg/m^2. After completion of enrollment into the Dose Confirmation Stage, 18-24 evaluable subjects will be randomized into a crossover study to confirm that the ASTX727 FDC yields PK exposures and DNA demethylation similar to those for IV decitabine.

Subjects will be randomized in a 1:1 ratio to receive the FDC tablet daily×5 in Course 1 followed by IV decitabine daily ×5 in Course 2, or the converse. In Courses ≥3, all subjects will receive the FDC tablet daily ×5 (in a 28-day course) until disease progression or unacceptable toxicity or withdrawal from the study.

Based on (1) data from both the Dose Escalation Stage and Dose Confirmation Stage, which confirmed that the combination doses of 100 mg E7727 + 35 mg decitabine emulate the PK and pharmacodynamics (PD) of IV

decitabine 20 mg/m^2, and (2) availability of the FDC tablet combining these 2 doses, subjects who are still on treatment with the separate E7727 and decitabine capsules in the previous study stages will be allowed to transition to treatment with the more convenient FDC tablet at the discretion of the investigator but no later than 23 October 2017. New clinical supplies of the E7727 and decitabine capsules will not be supported after the expiry date (31 October 2017) of the current supplies.

Study Population:

Number of Subjects

At least 3 evaluable subjects per cohort will be treated in the Dose Escalation Stage, at least 42 evaluable subjects will be treated in the Dose Confirmation Stage, and 18-24 evaluable subjects will be treated in the FDC Stage.

Inclusion Criteria

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 written informed consent before the first study-specific procedure.
2. Men or women ≥18 years with IPSS intermediate-1, intermediate-2 or high-risk MDS with peripheral blasts or bone marrow blasts <20% in all study stages, including subjects with chronic myelomonocytic leukemia (CMML) who are candidates for treatment with a hypomethylating agent.
3. Subjects with Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (see Appendix 3).
4. Subjects with adequate organ function defined as:
   a) Hepatic: Total or direct bilirubin ≤2 X ULN; AST/SGOT and ALT/SGPT ≤2.5 X ULN
   b) Renal: serum creatinine ≤1.5 X ULN or creatinine clearance >50 mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal
5. For subjects with prior allogeneic stem cell transplant, no evidence of graft-versus-host disease (GVHD) and must be ≥2 weeks off systemic immunosuppressive therapy.
6. Subjects with no major surgery within 2 weeks of first study treatment.
7. Subjects with no cytotoxic chemotherapy within 2 weeks of first study treatment.
8. 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 (FSH) levels in the menopausal range.
9. 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, double-barrier method (use of a condom AND diaphragm, with spermicide), or abstaining from sexual intercourse.
10. Able to swallow the number of capsules required for the treatment assignment within a 10-minute period and tolerate 4 hours of fasting.

Exclusion Criteria

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

1. Previous treatment with at least 2 courses of decitabine (all stages) or azacitidine (Dose Confirmation Stage).
2. Known or suspected hypersensitivity to decitabine or the components of E7727.
3. Treated with any investigational drug or therapy within 2 weeks of study treatment, or 5 half-lives, whichever is longer, before the protocol-defined first dose of study treatment, or ongoing clinically significant adverse events from previous treatment with investigational drug or therapy.
4. Poor medical risk because of other conditions such as uncontrolled systemic diseases or active uncontrolled infections.
5. Diagnosis of AML with bone marrow or peripheral blast count ≥20% or other hematological malignancies.
6. Life-threatening illness, medical condition or organ system dysfunction, 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 oral decitabine + E7727 or compromise the integrity of the study outcomes.

7. Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, non-metastatic prostate cancer with normal prostate-specific antigen (PSA), or other cancer from which the subject has been disease free for at least 3 years.
8. Known history of human immunodeficiency virus (HIV) or if known seropositive for hepatitis C virus (HCV) or hepatitis B virus (HBV).
9. Active uncontrolled gastric or duodenal ulcer.

Study Treatment:

IV decitabine 20 mg/m^2 is to be administered as a 1-hour intravenous infusion per the prescribing information. This dose level remains constant throughout the trial.

The starting dose levels for Cohort 1 in the Dose Escalation Stage are E7727 40 mg and oral decitabine 20 mg. Subjects will be fasting on days when receiving study treatment orally. Fasting (no food, milk or alcohol) is defined as 2 hours prior to the dose and at least 2 hours post-dose. Only clear liquids such as water, black coffee, tea, or fruit juice may be allowed as desired. Administer oral doses with 240 mL (8 fluid oz) of water. Subjects should take the investigational medicinal products (IMPs) simultaneously (ie, E7727 followed immediately by oral decitabine). The IMPs should be taken at the same time of day (±1 hour) on each dosing day, in at least the first 2 courses of treatment. When oral decitabine or E7727 is given alone (Day -3 ±2 days of Courses 1 and 2), each will be administered at the same dose it is scheduled to be given when the IMPs are combined on subsequent days in the same course.

The ASTX727 FDC tablet is to be administered in the manner described above regarding fasting, administration with water, and administration at the same time of day.

Study Endpoints:

Dose Escalation Stage

Primary Endpoint

- Mean decitabine AUC oral/IV: Mean AUC of oral decitabine given with E7727 (Days 2 and/or 5) compared with IV decitabine 20 mg/m^2 (Day 1).
- Incidence and severity grades of DLTs.

Secondary Endpoints

- AUC, C_{max}, T_{max}, and other PK parameters of oral decitabine, E7727, and E7727-epimer.
- Incidence and severity of adverse events and clinically significant abnormal laboratory values
- Mean maximum %LINE-1 demethylation of oral decitabine + E7727 by cohort.
- Overall response rate as measured by the IWG 2006 MDS Response Criteria, duration of response, hematological improvement, rate of transfusion independence, time to AML, and overall survival.

Exploratory Endpoint

[redacted]

Dose Confirmation Stage

Primary Endpoints

- Mean decitabine AUC (estimated from 5 days of dosing) and mean maximum %LINE-1 demethylation after oral decitabine + E7727 compared with IV decitabine 20 mg/m^2.
- Response rate in all subjects.

Secondary Endpoints

- Incidence and severity grades of adverse events (AEs) and clinically significant abnormal laboratory values.
- Duration of response, hematological improvement, rate of transfusion independence, time to AML, and overall survival.
- Other PK parameters of oral decitabine, E7727, and E7727-epimer (if needed).

Exploratory Endpoint

- [redacted].

Fixed-Dose Combination Stage

Primary Endpoints

- Mean decitabine AUC and mean maximum %LINE-1 demethylation after ASTX727 administration compared with IV decitabine 20 mg/m^2.
- Response rate in all subjects.

Secondary Endpoints

- Incidence and severity grades of AEs and clinically significant abnormal laboratory values.
- Duration of response, hematological improvement, rate of transfusion independence, time to AML, and overall survival.
- Other PK parameters of ASTX727.

Exploratory Endpoint

- [redacted].

Study Assessments and Procedures (see Section 9.0 and Table 3 through Table 6 for details):

- **Screening Assessments:** Baseline assessment of eligibility criteria, physical examination and medical history including demographics, hematology, chemistry, urinalysis, ECG, ECHO/MUGA, and bone marrow aspirate or biopsy.
- **Efficacy Assessments:** Efficacy assessments (via bone marrow aspirate or biopsy) will be based on the IWG 2006 MDS Response Criteria for MDS.
- **PK:** AUC, C_{max}, T_{max}, and other PK parameters of decitabine, E7727, and E7727-epimer.
- **Pharmacodynamics:** In all subjects, global LINE-1 DNA methylation will be assessed at Screening, and at specified times (see Schedule of Events) after Course 1, and Course 2.

Safety Assessments: Safety will be assessed by subject reported and Investigator observed AEs along with physical examination clinical laboratory tests (hematology, chemistries, and urinalysis) and ECG. DLTs will be determined during the first course of treatment as defined in Section 4.5 (Dose Escalation Stage only).

Subjects ongoing in the Dose Escalation Stage or Dose Confirmation Stage who transition from the E7727 + decitabine capsules to the ASTX727 FDC tablet will continue with all study assessments and procedures as indicated for the FDC Stage.

Sample Size and Statistical Analyses:

Sample Size for Dose Escalation Stage

At least 3 evaluable subjects will be treated in each cohort to allow sufficient decitabine PK (AUC) data comparison between IV decitabine at the approved dose of 20 mg/m^2 (Course 1 Day 1) and the different dose levels of oral decitabine + E7727 (decitabine AUC Day 2 and/or Day 5 after oral administration). Up to 6 additional evaluable subjects may be enrolled in a cohort before PK and safety results from at least the first 3 subjects in that cohort become available. When the AUC range for a 3-subject cohort is between 0.90-1.10 of IV decitabine, and no more than 1 DLT has occurred, additional evaluable subjects may be added to reach up to 12 -18 subjects in that cohort) to confirm the AUC range at 0.90-1.10 and to confirm safety at no more than 1 DLT in 6 subjects. If AUC and safety are confirmed in those 12 subjects, the Dose Confirmation Stage of the trial will be opened. Otherwise, the dose of E7727 or decitabine will be titrated further (escalated or de-escalated) based on AUC and safety until the AUC is confirmed at 0.90-1.10 and safety is confirmed at no more than 1 DLT in 6 subjects.

Sample Size for Dose Confirmation Stage

Approximately 42 evaluable subjects are planned for enrollment into the Dose Confirmation Stage at the final recommended dose combination. Data from these subjects will be primarily used to assess decitabine AUC and LINE-1 demethylation, using a standard 2 x 2 cross-over design (the first 2 courses), between IV decitabine 20 mg/m^2 daily×5 and the final recommended doses of oral decitabine + E7727.

Sample Size for Fixed-Dose Combination Stage

In an equivalence test of the mean decitabine AUCs of the ASTX727 FDC tablet compared with IV decitabine, data from the 18-24 evaluable subjects in a standard 2 x 2 crossover design will provide 75%-88% power at a 10% significance level using 2 one-sided tests when the true ratio of means is 1.0, the coefficient of variation under an unlogged scale is 0.55, and the equivalence limits for the ratio of means are 0.65 and 1.539. The sample size of 18-24 evaluable subjects in the same 2 x 2 crossover design achieves 78%-86% power to detect non-inferiority in the comparison of mean maximum %LINE-1 demethylation from baseline between the FDC tablet and IV decitabine using a one-sided t-test when the margin of non-inferiority is -0.075, the true mean difference is 0, the standard deviation is 0.15, and the significance level is 0.1.

Efficacy Analyses:

Response rates and rates of hematologic improvement will be calculated as defined by the IWG 2006 MDS Response Criteria. Rates of transfusion independence will be calculated based on the number of transfusion-dependent subjects who had no transfusion for at least 56 days during treatment.

Overall survival will be defined as the number of days from the day the subject received the first dose of study treatment to the date of death (regardless of cause). Time to AML will be the number of days from the day the subject received the first dose of study treatment to the date of MDS progression to AML as defined by ≥20% blasts in bone marrow or peripheral blood, or death.

Pharmacokinetics/Pharmacodynamics Analyses:

PK parameters will be summarized descriptively using mean, standard deviation, median and range by dose cohort and course/days, and by stage of the study if deemed necessary. PK values obtained after oral decitabine + E7727 will be compared with those after IV decitabine on an intra-subject basis and also by dose/cohort average basis. In addition, the decitabine AUC values obtained from the 2 x 2 crossover part of the study will be analyzed for comparability of means using the CI method (Section 11.8.1).

Pharmacodynamic (LINE-1 demethylation data) and biomarkers will be summarized descriptively (using mean, standard deviation, median and range for continuous variables and counts and percentages for categorical variables) by dose cohort and course/days, and by stage of the study. In addition, the mean maximum %LINE-1 demethylation from baseline obtained from the 2 x 2 crossover design part of the study will be analyzed for non-inferiority of means (oral decitabine + E7727 compared with IV decitabine) using the CI method (Section 11.8.2).

Safety Analyses:

Adverse events will be summarized using counts and percentages by MedDRA System Organ Class (SOC) and Preferred Term (PT) and by CTCAE grades. DLTs will be identified in each dose cohort (as defined in Section 4.5) and listed separately to assist in determining the desired dose level for the combination of oral decitabine + E7727 in the Dose Escalation Stage. Concomitant medications will be summarized by WHO Drug Therapeutic subgroup and generic name. Clinical laboratory values will be listed and reviewed.

Interim Analysis:

No formal interim analysis is planned for this study. However, ongoing data review will be performed by the Data and Safety Review Committee (DSRC) as described in Section 4.4.

Study Duration and Termination:

The expected study duration is as follows:

Dose Escalation Stage ≈12 months

Dose Confirmation Stage ≈12 months

Fixed-Dose Combination Stage ≈ 12 months

The study is expected to begin (ie, first subject enrolled) in 2Q14.

Compliance Statement:

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, US Title 21 CFR Parts 11, 50, 54, 56, and 312; and the principles enunciated in the Declaration of Helsinki and all human clinical research regulations in the countries where the study is to be conducted.

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ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
ALT	Alanine transaminase (serum glutamic pyruvic transaminase [SGPT])
AML	Acute myelogenous leukemia
ANC	Absolute neutrophil count
AST	Aspartate transaminase (serum glutamic oxaloacetic transaminase [SGOT])
AUC	Area under the curve
BSA	Body surface area
BUN	Blood urea nitrogen
BW	Body weight
CBC	Complete blood count
CDA	Cytidine deaminase
CDAi	Cytidine deaminase inhibitor
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Plasma clearance
CL/F	Apparent plasma clearance
C_{max}	Maximum concentration
CMML	Chronic myelomonocytic leukemia
CPK	Creatine phosphokinase
CR	Complete response
CRF/eCRF	Case report form/electronic case report form
CRO	Contract research organization
CT scan	Computed tomography scan
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DNMT	DNA-methyltransferase
DSRC	Data and Safety Review Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
EMEA	Evaluation of Medicinal Products
ESA	Erythropoietin stimulating agents
EU	European Union
FAB	French-American-British
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FIH	First in human
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
GVHD	Graft-versus-host disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus

HDPE	High density polyethylene
HED	Human equivalent dose
HI	Hematological improvement
HIV	Human immunodeficiency virus
HMA	Hypomethylating agent
ICF	Informed consent form
ICH	International Conference on Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IMP	Investigational medicinal product (the specific Astex drug product under study)
IPSS	International Prognostic Scoring System
IRB	Institutional Review Board
IV	Intravenous
IWG	International Working Group
LINE-1	Long interspersed nucleotide elements-1
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
MUGA	Multi gated acquisition (scan)
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
OTC	Over the counter
PBMC	Peripheral blood mononuclear cells
PD	Pharmacodynamic(s)
PE	Physical examination
pH	a measure of the acidity or alkalinity of an aqueous solution
PK	Pharmacokinetic(s)
PR	Partial response
PRBCs	Packed red blood cells
PT	Preferred term
QD	Once daily
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
SQ	Subcutaneous
SUSAR	Serious unexpected suspected adverse reaction
$T_{1/2}$	Apparent elimination half-life
TEAE	Treatment emergent adverse event
THU	Tetrahydrouridine
T_{max}	Time at which C_{max} occurs
ULN	Upper limit of normal
V_D	Volume of distribution
V_D/F	Apparent volume of distribution
WHO	World Health Organization

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. 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 (Benjanyan 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-1) MDS (approximately 70% of patients) have an expected median survival of 3.5 to 5.7 years. Median survival for higher risk patients (intermediate-2 and high-risk MDS) ranges from 0.4 to 1.2 years (Greenberg et al 1997).

1.2 Background of Treatment Options

The standard for MDS therapy for many years has been supportive care (Heaney and Golde 1999; Kantarjian and Estey 2001). Intensive chemotherapy has been associated with complete response rates of 40% to 60%, induction mortality rates of 10% to 40% and no improvement in survival (Kantarjian and Estey 2001).

Within the previous 10 years, three agents have been approved by the US FDA for the treatment of MDS: the immunomodulating agent lenalidomide, and the hypomethylating agents (HMAs) azacitidine and decitabine. These agents have dramatically changed both the course of treatment for MDS and have improved the outcome of patients who previously had very poor survival. Patients administered azacitidine at a subcutaneous dose of 75 mg/m^2 daily×7 showed an overall response rate (CR+PR) of 15.7%, which was significantly greater than the response rate of 0% in the observation group ($p<0.0001$) (Vidaza 2016). Similarly, patients with intermediate- or high-risk MDS who were administered IV decitabine (Dacogen®) at a dose of 20 mg/m^2 daily×5 showed an overall response rate of 16% (Dacogen 2014).

In summary, the increasing use of azacitidine and decitabine in the treatment of MDS has improved the outcome of patients who previously had very poor survival. However, current marketed HMAs

are subject to rapid elimination and degradation by cytidine deaminase (CDA) into inactive uridine counterparts (Chabot et al 1983). CDA in the gut and liver is responsible for poor bioavailability of these two HMAs, thus limiting their use to intravenous (IV) or subcutaneous injections (Karahoca and Momparler 2013). CDA inhibitors (CDAi) have been investigated for many years, but no drug has been approved for this use. The most widely published use has been with the CDAi tetrahydrouridine or THU (Beumer et al 2011; Beumer, Eiseman et al 2008; Beumer et al 2006). National Cancer Institute (NCI) has been investigating THU along with DNA methyltransferase (DNMT) inhibitor 5-fluoro-2'-deoxycytidine in clinical trials (Beumer, Parise et al 2008). However, THU is an unstable compound that is difficult to develop into a pharmaceutically acceptable drug.

E7727 is a new potent CDAi which is pharmaceutically stable with a large safety margin. Its concomitant administration with oral decitabine markedly enhanced its bioavailability. This protocol intends to investigate the optimal dose of E7727 administered with oral decitabine that results in comparable AUC, Long Interspersed Nucleotide Elements-1 (LINE-1) demethylation, and response rate (CR+PR) to that of the approved IV decitabine 5-day regimen. The aim is to identify the relative doses to use as a fixed dose combination (FDC) oral product (ASTX727) of oral decitabine + E7727.

Availability of an oral form of decitabine should provide significant convenience and potentially better treatment compliance for MDS patients.

1.3 Summary of Nonclinical and Clinical Data for Oral Decitabine + E7727

Please refer to the Investigator's Brochure (IB) for ASTX727 for detailed information on the Investigational Medicinal Product (IMP). Detailed information on IV decitabine 5-day regimen can be reviewed in the US Dacogen IV Prescribing Information (2014).

1.3.1 General Information

Information on the IMP is located in Section 7.1.

1.3.2 Nonclinical Data

E7727 is a 2'-fluorinated analog of tetrahydrouridine (THU) and is a novel CDAi, developed for oral administration. The bioavailability of decitabine and of several other therapeutic cytidine analogs (eg, azacitidine, cytarabine, gemcitabine) is significantly limited by a rapid metabolism catalyzed by CDA which is highly expressed in the gut and liver. E7727 is a potent CDAi with an IC_{50} of 0.281 μM. E7727 is also characterized by an improved stability at lower pH which has been a challenge with THU.

E7727 has negligible antiproliferative activity in human cancer cell lines, did not show any significant inhibition in a panel of 80 physiologically important human receptors and did not inhibit hERG potassium channel at up to 300 μM. In vitro studies have also characterized an epimer of E7727 (ER-849726) that has about 1/10th the activity of E7727 as determined by an IC_{50} of

5 µM against human recombinant CDA. After oral dosing in preclinical toxicology models (mouse and monkey), near-equivalent levels were detected for circulating E7727 and its epimer.

Several in vitro safety pharmacology studies were performed with various concentrations of the CDAi E7727 and are summarized in Table 1.

Table 1: In Vitro Safety Pharmacology Studies

Title	System	Key Findings for 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 (Report NCLI-013195)	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 (Report PHAR 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) (Report PPC-2010-04)	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 (Report BIOL-2013-001)	Human cell lines	No significant inhibition of any cell line tested

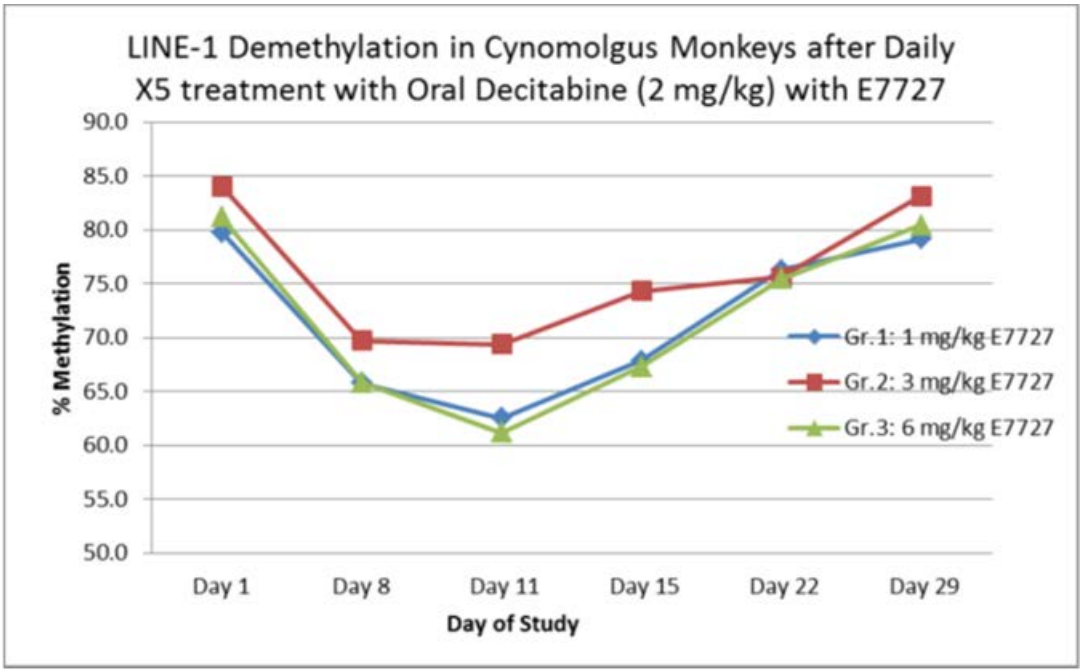
Several in vivo pharmacology studies were performed to determine the effect of E7727 on in vivo anticancer activity of oral decitabine and are summarized in Table 2.

Table 2: In Vivo Pharmacology Studies

Title	System	Key Findings for E7727
Effect of E7727 on in vivo anticancer activity of oral decitabine against CD2-F1 mouse L1210 disseminated model (Report NCLI-015044)	L1210 mouse ALL disseminated model	All 3 dose levels of E7727 (1, 10 and 100 mg/kg) + 0.4 mg/kg oral DAC have significant anti-tumor activity
Effect of E7727 on in vivo anticancer activity of oral decitabine against KG-1 human AML disseminated model (Report NCLI-014913)	KG-1 human AML disseminated model	All three doses of E7727 (1, 10 and 100 mg/kg) + 0.3 mg/kg oral DAC have significant anti-tumor activity

The pharmacodynamics (PD) of oral decitabine + E7727 were demonstrated in a one-cycle study in cynomolgus monkeys in which decitabine was administered at 2 mg/kg with E7727 doses of 1, 3, or 6 mg/kg daily×5, followed by 23 days. Demethylation of LINE-1 sequences was seen for all three treatment groups, with the maximum demethylation effect of 17.4% to 24.5% achieved on Day 11 (see Figure 1).

Figure 1: LINE-1 Demethylation in Cynomolgus Monkeys – Oral Decitabine 2 mg/kg + E7727 (1, 3, and 6 mg/kg) Daily×5



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

1.3.3 Clinical Data and Human Pharmacokinetics (PK)

Preliminary data from the current study were available at the time of Amendment 3 and were used to inform the strength of the active drug substance included in FDC tablet.

Previously, an open-label, Phase 1, dose-escalation trial was conducted to assess the preliminary oral bioavailability and safety of a single oral decitabine dose in an MDS patient population (Mistry et al 2011). Twelve subjects were enrolled in the study. Decitabine was administered orally (using the same formulation that is used for IV administration) on Day 1 of Course 1, followed by a 1-hour IV infusion at the recommended dose of 20 mg/m^2 on Days 2–5 of Course 1.

Biphasic elimination was observed following both IV and oral administration. Across the cohorts, $T_{½}$ was comparable and ranged from 0.35 to 0.79 hour following oral administration and from 0.34 to 0.61 hour following IV administration.

Decitabine was rapidly absorbed after oral administration; the mean T_{max} was 0.5 hour; however, oral doses from 30 mg to 120 mg did not result in increased C_{max} or AUC. At the 240 mg dose, abrupt increases in C_{max} and AUC of decitabine were observed.

The mean absolute bioavailability following 30, 60, 120, and 240 mg oral doses of decitabine was low, ranging from 3.9% to 14.1% with a very high intersubject variability. Single, oral doses of decitabine up to 240 mg were safe and generally well tolerated.

1.4 Potential Risks and Benefits to Human Subjects

Decitabine at therapeutic exposure levels is known to result in neutropenia, thrombocytopenia, anemia, and pyrexia. E7727 has a wide safety margin, as preclinical toxicology studies suggest that transient inhibition of CDA is well tolerated and poses no known risks, with the NOAEL in monkeys determined to be 200 mg/kg, dosed daily×7. The starting dose of E7727 in this first-in-human (FIH) study is 100-fold lower than the NOAEL (human equivalent dose [HED] to 2 mg/kg in monkeys).

The combination of E7727 with oral decitabine may result in enhanced decitabine exposure, which at high doses may result in higher hematological toxicity. In addition, administration of oral decitabine with E7727 may result in higher GI toxicity as a result of CDA inhibition in the gut or higher decitabine dose used. The starting dose of oral decitabine in this study is about half the IV decitabine dose (20 mg fixed oral dose as opposed to the approved daily dose of 20 mg/m^2 IV). It is also one-twelfth of the highest dose of oral decitabine (240 mg) tested in humans without E7727 (Mistry et al 2011).

These and other risks of oral decitabine + E7727 in humans are described further in Section 8.0, Risks/Precautions. For more detailed information, please refer to the IB for ASTX727 and to the prescribing information for decitabine (Dacogen 2014).

The potential benefits of oral decitabine + E7727 include a significant enhancement of the oral bioavailability of decitabine through inhibition of CDA the enzyme responsible for metabolism of decitabine in the gastrointestinal (GI) tract and liver. This will provide patients with more convenient regimen with at least similar therapeutic benefits to the approved IV decitabine regimen.

2.0 RATIONALE

2.1 Rationale for the Study

Astex Pharmaceuticals, Inc. is proposing a program to develop an oral, fixed-dose combination IMP, composed of oral decitabine + E7727 (ie, ASTX727) for the treatment of patients with MDS. Decitabine is one of 2 HMAs approved by FDA for this use. E7727 is a new chemical entity that is a pharmacokinetic (PK) enhancer. It increases bioavailability of decitabine through inhibition of CDA, an enzyme responsible for metabolism of decitabine in the GI tract and liver, thus enabling enhanced decitabine exposures after oral administration. E7727 is a potent and selective CDAi that has a wide safety margin and is pharmaceutically stable and suitable for oral use.

This FIH trial is designed to define daily doses of the individual components so that decitabine exposure after oral administration is comparable to exposure after IV decitabine at the approved

daily dose of 20 mg/m^2. The objective of the study is to establish and then confirm the doses of the 2 components to be used in the final fixed-drug combination product (ASTX727) using mainly PK (AUC) and PD (global DNA methylation in PBMCs using LINE-1) as endpoints. The doses that produce human exposure and/or PD comparable to that obtained after IV administration of decitabine at the approved daily dose using the 5-day schedule will be selected for use in subsequent clinical investigation.

2.2 Rationale for Oral Decitabine + E7727 Dose and Study Treatment Regimen

The selection of the starting dose of E7727 is based on findings from GLP toxicology studies that were conducted in mice and monkeys to evaluate the non-clinical safety profile of E7727 together with PK data in animals regarding E7727 doses needed to enhance decitabine exposure after oral administration.

E7727 appeared to be well tolerated in CD-1 mice, with no observed adverse effects seen at the highest dose tested (1000 mg/kg). Exposures at the no observed adverse effect level (NOAEL) of 1000 mg/kg (highest dose tested) were similar in males and females. The C_{max} after 1000 mg/kg was approximately 43,700 ng/mL and the AUC_{0-24} was ~ 125,600 ng*hour/mL.

In rhesus monkeys, the NOAEL was 200 mg/kg/d from a 7-day repeat-dose study with a 2-week recovery. No accumulation or gender differences were seen in exposures. On Day 7, the C_{max} at this dose ranged from 5,746-6,148 ng/mL, and AUC_{0-24} was 33,457-46,214 ng*hour/mL.

In the Dose Escalation Stage, the starting dose for E7727 is based upon the NOAEL from monkeys (200 mg/kg), as well as the PK data from the oral decitabine + E7727 interaction studies in cynomolgus monkeys, wherein a significant effect on oral decitabine exposures was seen at E7727 doses as low as 0.1 mg/kg when E7727 is given 1 hour before decitabine, and at 1-3 mg/kg with concomitant dosing. The proposed starting E7727 dose of 40 mg is approximately the HED of E7727 given at 2 mg/kg for monkeys (equivalent to 24 mg/m^2 in humans) and offers a 100-fold safety margin relative to NOAEL from a GLP toxicology study in monkeys.

As the clinical safety profile for decitabine is already well understood, the starting dose of 20 mg is based upon the available human experience with single dose decitabine and the experience with approved IV daily doses as the basis for the starting dose of decitabine in this study. The approved 5-day daily dose is 20 mg/m^2 IV or 40 mg for a BSA of 2 m^2. The clinical study that assessed PK and safety of single oral dose decitabine (30-240 mg) showed no safety issues up to 240 mg. We propose a starting dose of oral decitabine of 20 mg, which is approximately one-half of the approved IV daily dose (for a BSA of 2 m^2), and one-twelfth of the highest oral decitabine dose (240 mg) tested in humans (Mistry et al 2011).

Thus, the proposed starting dose combination is 40 mg E7727 and 20 mg decitabine given concomitantly by mouth.

Preliminary PK data from both the Dose Escalation Stage and Dose Confirmation Stage informed selection of the strength of the FDC tablet.

3.0 STUDY OBJECTIVES

3.1 Dose Escalation Stage - Primary Objectives

- Assess safety, tolerability, and pharmacokinetics (PK) of concomitant orally administered decitabine + E7727.
- Identify a dose of oral decitabine + E7727 that together achieve a target mean decitabine AUC comparable to that from decitabine given by IV infusion (20 mg/m^2) for 1 hour.

3.2 Dose Escalation Stage - Secondary Objectives

- Determine percent change of LINE-1 demethylation in Course 1 and Course 2.
- Assess preliminary efficacy, as determined by response rate, duration of response, hematological improvement, rate of transfusion independence, time to AML, and overall survival.
- Evaluate other PK parameters of decitabine, E7727, and E7727-epimer.

3.3 Dose Escalation Stage - Exploratory Objectives

[redacted]

3.4 Dose Confirmation Stage - Primary Objectives

- Confirm the dose of oral decitabine + E7727 identified in the Dose Escalation Stage administered daily×5 that achieves mean decitabine AUC (estimated from 5 days of dosing) and LINE-1 DNA demethylation comparable to that of IV decitabine 20 mg/m^2 daily×5.
- Assess response rate in all subjects.

3.5 Dose Confirmation Stage - Secondary Objectives

- Assess safety and tolerability of oral decitabine + E7727.
- Assess duration of response, hematological improvement, rate of transfusion independence, time to AML, and overall survival.
- Evaluate other PK parameters of oral decitabine, E7727, and E7727-epimer (if needed).

3.6 Dose Confirmation Stage - Exploratory Objective

[redacted]

3.7 Fixed-Dose Combination Stage - Primary Objectives

- Confirm the ASTX727 FDC tablet achieves mean decitabine AUC (estimated from 5 days of dosing) and LINE-1 DNA demethylation similar to that for IV decitabine 20 mg/m^2 daily×5.

- Assess response rate in all subjects.

3.8 Fixed-Dose Combination Stage - Secondary Objectives

- Assess safety and tolerability of ASTX727.
- Assess duration of response, hematological improvement, rate of transfusion independence, time to AML, and overall survival.
- Evaluate other PK parameters of ASTX727.

3.9 Fixed-Dose Combination Stage - Exploratory Objective

[redacted]

4.0 INVESTIGATIONAL PLAN

4.1 Overall Study Design

Study ASTX727-01 will consist of three stages: Dose Escalation, Dose Confirmation, and Fixed-Dose Combination, accordingly described below.

4.1.1 Dose Escalation Stage

The Dose Escalation Stage consists of a single arm PK guided 3+3 design, the objective of which is to establish the target dose combination of oral decitabine + E7727 administered concomitantly using PK (AUC) as an endpoint.

The starting dose for cohort 1 for E7727 is 40 mg, and the starting dose of oral decitabine is 20 mg. All subsequent cohort dose levels and cohort sizes will be determined by the Data and Safety Review Committee (DSRC) based on both safety and PK data review from at least 3 evaluable subjects in each cohort; see below for dose escalation guidance and Section 4.4 for description of DSRC functions.

The dosing schedule for all cohorts in the Dose Escalation Stage is as follows:

Course 1:

- Day -3 (± 2 days): Single dose oral decitabine.
- Day 1: IV decitabine administered at 20 mg/m^2.
- Days 2-5: Concomitant oral administration of oral decitabine + E7727.

Course 2:

- Day -3 (± 2 days): Single dose E7727.
- Days 1-5: Concomitant oral administration of E7727 + decitabine.

The doses of single oral decitabine or oral E7727 given on Day -3 (±2 days) in Course 1 and Course 2 are the same doses, respectively, that are given concomitantly on Days 2-5 in Course 1 and Days 1-5 in Course 2.

Course ≥3:

- Days 1-5: Concomitant oral administration of E7727 + decitabine (note, there are no Day -3 visits beginning with Course 3).

All subjects will continue to receive oral decitabine + E7727 daily×5 of a 28-day course in Course 3 and thereafter until disease progression, unacceptable toxicity, subject withdrawal of consent, or withdrawal from the study.

Dosing for Cohort ≥2:

The dosing schedule for Cohort ≥2 will be the same as for Cohort 1; however, the dose levels of either E7727 or oral decitabine will be modified based on the decision of the DSRC guided by the algorithm in Figure 2. Only one of the 2 components will be escalated at any one time. If 1 DLT occurs in the first 3 subjects in the cohort, 3 more subjects will be added in that cohort to assess safety and AUC range. In the absence of Dose Limiting Toxicities (DLTs) in more than 1 of the first 6 subjects in any cohort, the dose of E7727 will be escalated in 20 mg increments until the cohort mean decitabine oral AUC/IV decitabine AUC approaches unity (within 0.90-1.10, inclusive). If E7727 dose adjustments fail to produce the desired oral decitabine AUC levels, or that smaller dose adjustment is required (5 mg instead of 20 mg), the decitabine dose (increments or decrements of 20 mg or 5 mg) will be adjusted until the desired AUC levels are achieved.

- If decitabine exposures in Cohort 1 are less than 0.90 of those achieved with IV infusion from Day 1, increase the E7727 dose by 20 mg increments until decitabine exposures no longer increase; then increase the decitabine dose by 20 mg or less until the desired AUC range of oral decitabine (0.90-1.10 of IV decitabine) is achieved.
- If oral decitabine AUC exposures in any cohort are more than 1.1 of the IV decitabine AUC, then decrease the E7727 dose by 20 mg or decrease decitabine doses by 20 mg or less until the desired AUC range of oral decitabine (0.90-1.10 of IV decitabine) is achieved.

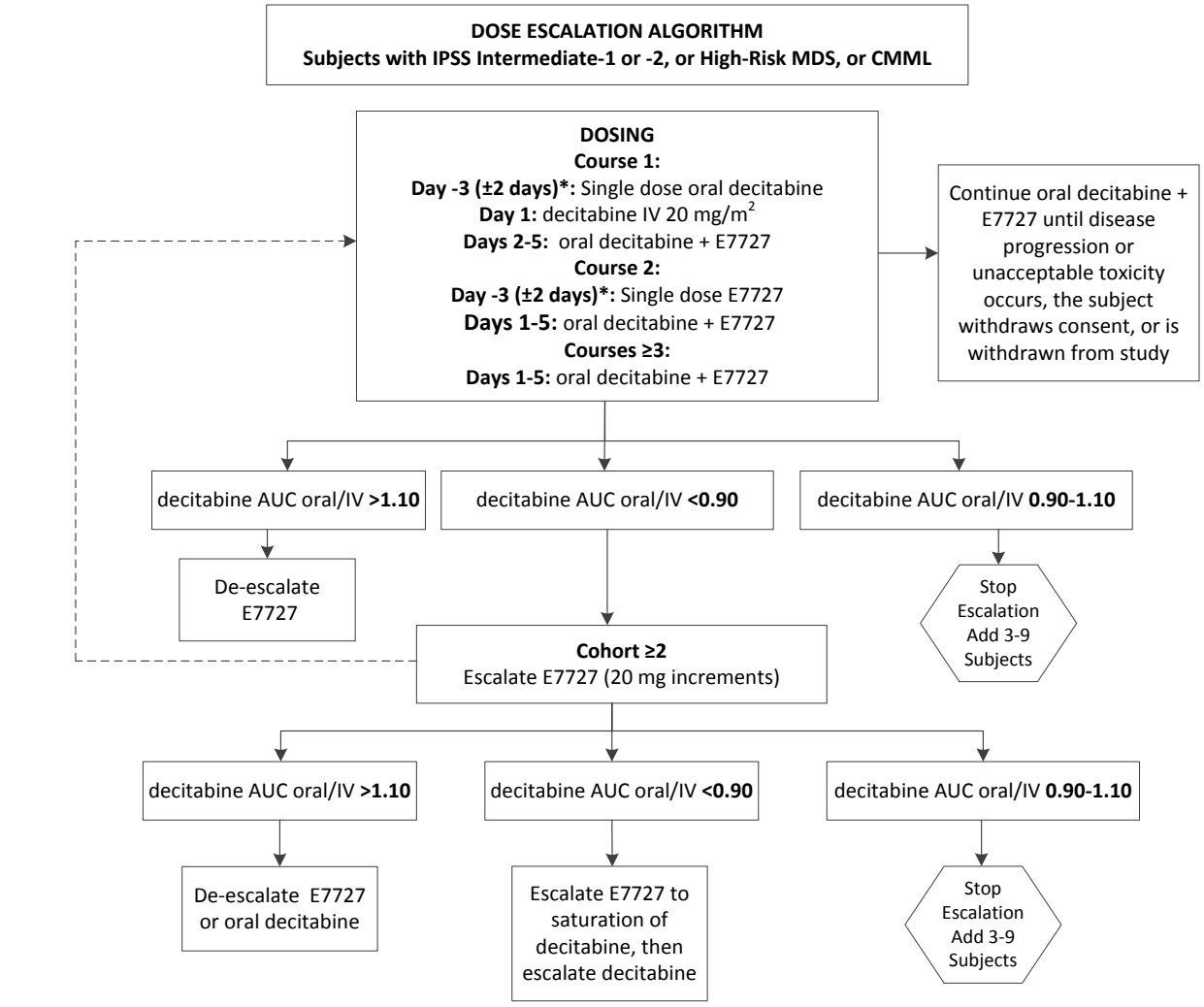
When the target level of decitabine AUC after oral administration is within 0.90-1.10 of IV decitabine AUC with no more than 1 DLT in 3-6 evaluable subjects, additional evaluable subjects may be added to the cohort to reach up to 12-18 subjects in that cohort to confirm the AUC range at 0.90-1.10 before opening the Dose Confirmation Stage of the trial. If the AUC range in the first 12 subjects is out of the desired range, or more than 1 DLT occurred in 6 subjects, the DSRC can recommend further adjustment of the E7727 or decitabine dose in a new cohort of at least 3 subjects until the desired AUC range (0.90-1.10) and safety (no more than 1 DLT) are achieved. If more than one DLT in 6 subjects is observed in any cohort, no further escalation will take place, and the DSRC will decide whether de-escalation of one or more components (oral decitabine and/or E7727) is necessary.

Intra-patient dose escalation will be allowed for patients who are still on treatment at lower dose levels in the Dose Escalation Stage once higher levels are deemed to be safe by DSRC review.

Figure 2 provides a suggested algorithm for dose escalation; however, the DSRC may deviate from that algorithm based on review of emerging safety and PK data as long as there is a consensus that it is safe to do so.

Up to 6 evaluable subjects may be enrolled in a cohort before PK and safety results from at least the first 3 subjects in that cohort become available.

Figure 2: Dose Escalation Stage Algorithm



When the target level of decitabine AUC after oral administration is within 0.90-1.10 of IV decitabine AUC with no more than 1 DLT, additional subjects may be added to the cohort (to reach up to 12-18 subjects in the cohort) to confirm the AUC range at 0.90-1.10 before opening the Dose Confirmation Stage. If the AUC is out of the desired range, or more than 1 DLT occurs in the first 12 subjects, the DSRC can recommend further adjustment of the E7727 or decitabine dose in a new cohort of 3 subjects until the desired AUC range and safety are achieved in at least 3 subjects.

*The doses of oral decitabine or oral E7727 given on Day -3 (±2 days) in Course 1 and Course 2 are the same doses, respectively, that are given on Days 2-5 in each cohort.

4.1.2 Dose Confirmation Stage

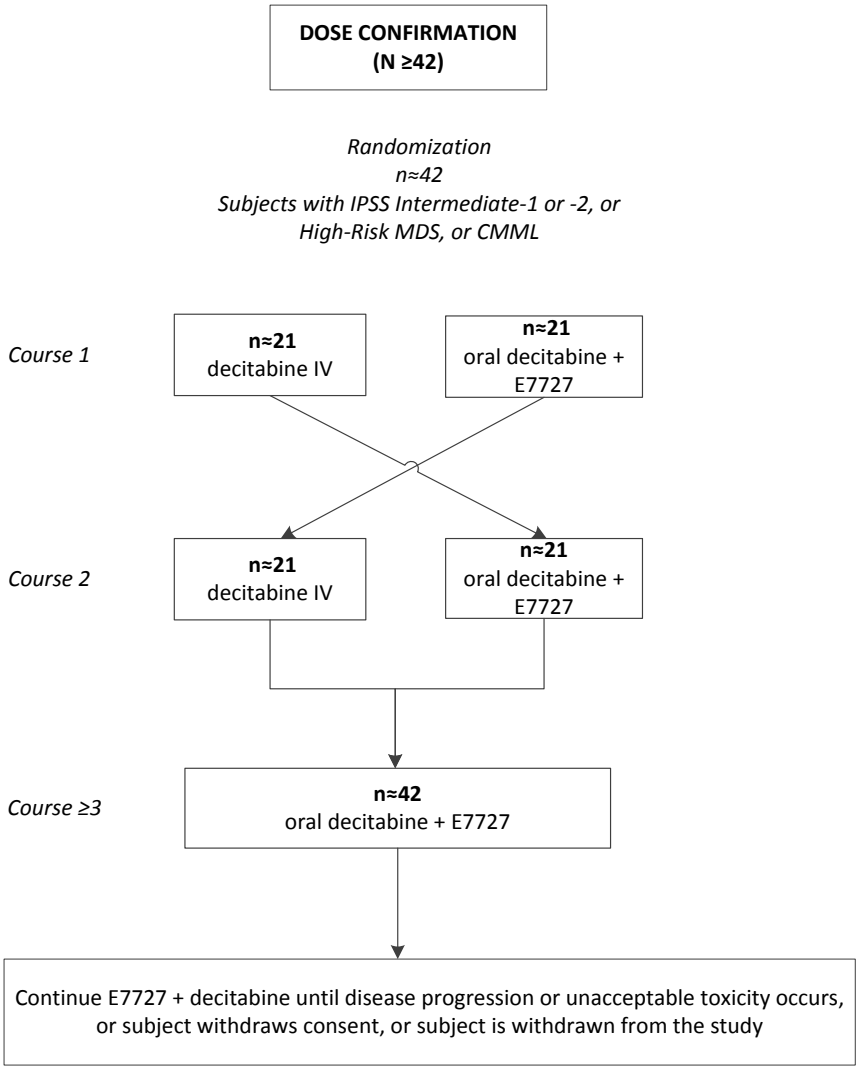
Dose Confirmation Stage (Figure 3) will confirm the dose level of oral decitabine + E7727 established in the Dose Escalation Stage in at least 42 evaluable subjects. Subjects will be randomized to the sequence of

- Oral decitabine + E7727 daily×5 in Course 1 followed by IV decitabine daily×5 in Course 2, or
- IV decitabine daily×5 in Course 1 followed by oral decitabine + E7727 daily×5 in Course 2.

Beginning with Course 3 and all subsequent courses, subjects will receive oral decitabine + E7727 daily×5 of a 28-day course until the subject has disease progression or unacceptable toxicity, or the subject withdraws consent or is withdrawn from the study.

The DSRC will determine when sufficient data are available at the end of the Dose Escalation Stage to make a decision on the fixed dose levels of E7727 and oral decitabine to be further investigated in the Dose Confirmation Stage.

Figure 3: Dose Confirmation Stage Schema

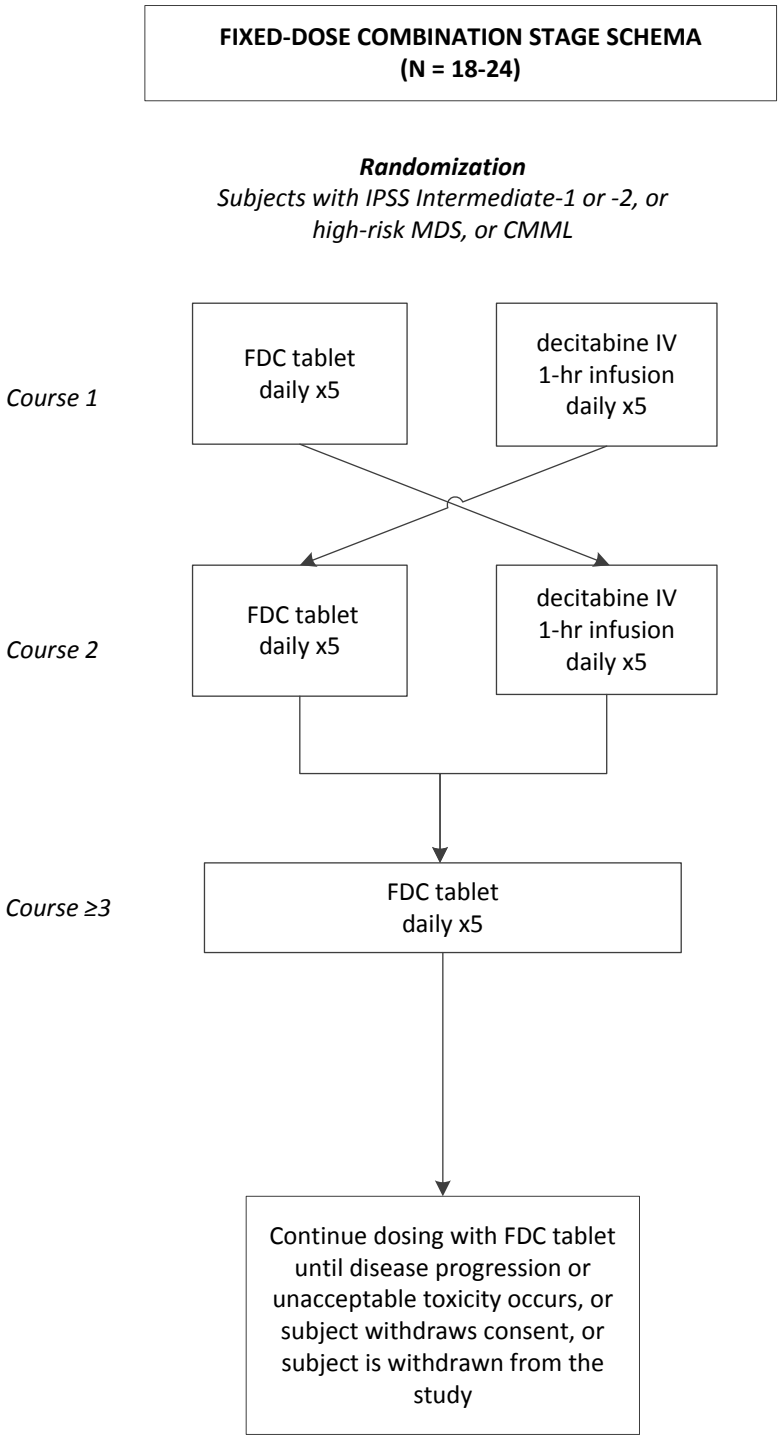


4.1.3 Fixed-Dose Combination Stage

This stage is a comparison between a tablet form of ASTX727 and IV decitabine 20 mg/m^2. After enrollment in the Dose Confirmation Stage has completed, 18-24 subjects will be randomized and treated in a crossover study to confirm that the ASTX727 FDC yields PK exposures and DNA demethylation similar to those for IV decitabine.

Subjects will be randomized in a 1:1 ratio to receive the FDC tablet daily ×5 in Course 1 followed by IV decitabine daily ×5 in Course 2, or the converse. In Courses ≥3, all subjects will receive the FDC tablet daily ×5 (in a 28-day course) until disease progression or unacceptable toxicity or withdrawal from the study. See Figure 4.

Figure 4: Fixed-Dose Combination Stage Schema



Based on (1) data from both the Dose Escalation Stage and Dose Confirmation Stage, which confirmed that the combination doses of 100 mg E7727 + 35 mg decitabine emulate the PK and PD of IV decitabine 20 mg/m^2, and (2) availability of the FDC tablet combining these 2 doses, subjects who are still on treatment with the separate E7727 and decitabine capsules in the previous study stages will be allowed to transition to treatment with the more convenient FDC tablet at the discretion of the investigator, but no later than 23 October 2017. New clinical supplies of the E7727 and decitabine capsules will not be supported after the expiry date (31 October 2017) of current supplies.

4.2 Discussion of Study Design

This is a 3-stage study to investigate concomitant administration of oral decitabine + E7727. The Dose Escalation Stage consists of a single arm PK guided 3+3 design, the objective of which is to establish the target dose combination of oral decitabine + E7727 administered concomitantly using PK (AUC) as an endpoint. The study is not intended to identify an MTD of oral decitabine + E7727. Rather, dose escalation will target a dose of the two components that approximately achieves unity in decitabine AUC exposures compared with AUC of IV decitabine 20 mg/m^2 (AUC ratio within 0.90-1.10). Escalation will occur only after review of the PK and safety data from at least 3 evaluable subjects in each cohort and a recommendation from the DSRC (see Section 4.4).

In the Dose Confirmation Stage, the primary objective is to confirm that the doses of oral decitabine + E7727 identified in the Dose Escalation Stage given as a daily×5 oral dosing regimen achieve a mean AUC (estimated from 5 days of dosing) and LINE-1 DNA demethylation comparable (as described in Sections 11.8.1 and 11.8.2) to IV decitabine given daily×5 at the approved dose of 20 mg/m^2. The standard 2 x 2 crossover design was chosen for the first two courses of the Dose Confirmation Stage in order to facilitate efficient evaluation of within-subject comparison of AUC as well as LINE-1 demethylation between oral decitabine + E7727 and IV decitabine. Because of the short half-life of decitabine and the fact that in most subjects, LINE-1 demethylation returns to baseline by Day 28 at the end of treatment course, no appreciable carry-over effect of either AUC or LINE-1 demethylation is expected.

In the FDC stage, the goal is to confirm that the FDC tablet formulation is similar to IV decitabine in an intrapatient fashion and that PK and PD results are similar to results obtained with oral decitabine + E7727 capsules in the Dose Confirmation Stage.

4.3 Study Endpoints

4.3.1 Dose Escalation Stage – Primary Endpoint

- Mean decitabine AUC oral/IV: Mean AUC of oral decitabine + E7727 (Days 2 and/or 5) compared with IV decitabine 20 mg/m^2 (Day 1).
- Incidence and severity grades of DLTs.

4.3.2 Dose Escalation Stage – Secondary Endpoints

- AUC, C_{max}, T_{max}, and other PK parameters of oral decitabine, E7727, and E7727-epimer.
- Overall incidence and severity of adverse events and clinically significant abnormal laboratory values.
- Mean maximum %LINE-1 demethylation of oral decitabine + E7727 by cohort.
- Overall response rate as measured by the IWG 2006 MDS Response Criteria, duration of response, hematological improvement, rate of transfusion independence, time to AML, and overall survival.

4.3.3 Dose Escalation Stage – Exploratory Endpoints

[redacted]

4.3.4 Dose Confirmation Stage – Primary Endpoints

- Mean decitabine AUC (estimated from 5 days of dosing) and mean maximum %LINE-1 demethylation after oral decitabine + E7727 compared with IV decitabine 20 mg/m^2.
- Response rate in all subjects.

4.3.5 Dose Confirmation Stage – Secondary Endpoints

- Incidence and severity grades of adverse events and clinically significant abnormal laboratory values.
- Duration of response, hematological improvement, rate of transfusion independence, time to AML, and overall survival.
- Other PK parameters of oral decitabine, E7727, and E7727-epimer (if needed).

4.3.6 Dose Confirmation Stage – Exploratory Endpoint

[redacted]

4.3.7 Fixed-Dose Combination Stage – Primary Endpoints

- Mean decitabine AUC and mean maximum %LINE-1 demethylation after ASTX727 administration compared with IV decitabine 20 mg/m^2.
- Response rate in all subjects.

4.3.8 Fixed-Dose Combination Stage – Secondary Endpoints

- Incidence and severity grades of AEs and clinically significant abnormal laboratory values.
- Duration of response, hematological improvement, rate of transfusion independence, time to AML, and overall survival.
- Other PK parameters of ASTX727.

4.3.9 Fixed-Dose Combination Stage – Exploratory Endpoints

[redacted]

4.4 Data and Safety Review Committee (DSRC)

A thorough review of PK and safety data by the DSRC will be regularly conducted, particularly at the following time points:

- After every cohort of 3-12 evaluable subjects during the Dose Escalation Stage.
- At the end the Dose Escalation Stage but before the Dose Confirmation Stage.
- At least quarterly during the Dose Confirmation Stage.
- At minimum after 18-24 subjects have received 2 courses of treatment in the FDC stage.

The DSRC will confer when the last of at least 3 evaluable subjects in a cohort completes Course 1, Day 28. If warranted, the committee may meet more frequently should there be any emergent safety issues. This committee will comprise the principal investigators (or nominated deputies), medical monitor, study director, PK director, and other study team members as appropriate and will review available safety, PK, and PD data. The DSRC will recommend whether to continue dosing based on the oral decitabine + E7727 dose escalation algorithm (Figure 2) and the safety data (DLTs). The DSRC may decide to increase any cohort size up to a total of 12-18 subjects to further assess the PK and/or safety signal. No dose escalation/de-escalation will ensue until the DSRC meets and concurs. The DSRC will make decisions regarding continuing dose escalation or de-escalation, to better assess the PK and safety of oral decitabine + E7727 during the Dose Escalation Stage. The DSRC will decide on the exact next dose level based on the escalation scheme provided in Figure 2. The DSRC may also decide to investigate smaller increments or decrements of oral decitabine when lower strength (decitabine 5 mg) becomes available. DSRC may also decide to escalate/de-escalate either drug component (E7727 or oral decitabine) if AUC levels or safety data at any cohort warrant such escalation/de-escalation.

The DSRC will determine when sufficient PK data are available at the end of the Dose Escalation Stage to make a decision on the fixed dose levels of E7727 and oral decitabine to be further investigated in the Dose Confirmation Stage. If population PK analyses suggest that dose levels of E7727 and oral decitabine are better adjusted based on body weight/body surface area (BW/BSA) instead of the initially recommended flat dosing in this protocol, the DSRC will determine the different dose strengths for subjects based on their BW or BSA.

In addition, the DSRC will evaluate safety, PK, and PD data during the Dose Confirmation Stage to assess AUC and LINE-1 demethylation comparability between IV decitabine and the combination of E7727 + oral decitabine and to determine the final oral dose combination. This will be evaluated after the first subset of 6-12 subjects are randomized in the Dose Confirmation Stage and their PK and PD data from the first 2 completed courses become available. The DSRC may decide to further titrate the doses (up or down) of one or both ASTX727 drug components

(oral decitabine or E7727) to ensure comparability of PK and PD with decitabine IV. In that case, another evaluation of PK and PD data from an additional 6-12 evaluable subjects will be conducted. The DSRC may decide on a final dose combination that yields an AUC for oral decitabine marginally beyond the 0.90-1.10 window of IV decitabine AUC with supportive data. Approximately 42 subjects will be treated at the final recommended dose combination; therefore the total number of subjects in the Dose Confirmation Stage may be more than 42 if the initial dose combinations at the start of the Dose Confirmation Stage were not the final recommended doses.

A formal record of each discussion will be kept and distributed to all study sites.

4.5 Definition of Dose-Limiting Toxicities

While this study is not intended to define an MTD of oral decitabine + E7727, dose-limiting toxicities must be assessed to confirm that it is safe to escalate based on AUC data comparability with the approved IV decitabine dosing.

The DLT occurring in the first course of treatment for all subjects at any cohort during dose escalation will guide the dose escalation decision. At subsequent courses, DLTs will guide dose adjustment or dose delays as discussed in Section 7.3. DLTs are defined using the Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0) (Appendix 1).

- ≥ Grade 3 non-hematologic toxicity (unless the DSRC determines that it is clearly related to an underlying disease or to disease progression), except the following:
  - Grade 3 nausea or vomiting that is controllable by anti-emetics.
  - Grade 3 diarrhea controllable by optimal therapy such as loperamide.
- Grade 3 laboratory tests other than serum creatinine, bilirubin, AST, or ALT will not be considered a DLT unless the abnormal result(s) is/are associated with clinical manifestations.
- Related prolonged Grade 4 thrombocytopenia that was not present prior to dosing, does not resolve within 14 days, and is not related to underlying disease.
- Related febrile neutropenia or Grade 4 neutropenia that was not present prior to dosing, does not resolve within 14 days, and is not related to underlying disease.
- Any toxicity (related to study treatment) that results in treatment delays of >4 weeks after Day 28.

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Number of Subjects and Centers

The Dose Escalation Stage is based on a 3+3 design, and the Dose Confirmation Stage is based on at least 42 evaluable subjects at the final recommended dose combination, to be enrolled at multiple centers.

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 written informed consent before the first study-specific procedure.
2) Men or women ≥18 years with IPSS intermediate-1, intermediate-2, or high risk MDS with peripheral blasts or bone marrow blasts <20% in all study stages, including subjects with chronic myelomonocytic leukemia (CMML) who are candidates for treatment with a hypomethylating agent.
3) Subjects with Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (see Appendix 3).
4) Subjects with adequate organ function defined as:
    a) Hepatic: Total or direct bilirubin ≤2 X ULN; AST/SGOT and ALT/SGPT ≤2.5 X ULN.
    a) Renal: serum creatinine ≤1.5 X ULN or creatinine clearance >50 mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal.
5) For subjects with prior allogeneic stem cell transplant, no evidence of graft-versus-host disease (GVHD) and must be ≥2 weeks off systemic immunosuppressive therapy.
6) Subjects with no major surgery within 2 weeks of first dose of study treatment.
7) Subjects with no cytotoxic chemotherapy within 2 weeks of first dose of study treatment.
8) 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 (FSH) levels in the menopausal range.
9) 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, double-barrier method (use of a condom AND diaphragm, with spermicide), or abstaining from sexual intercourse.
10) Able to swallow the number of capsules required for the treatment assignment within a 10-minute period and tolerate 4 hours of fasting.

5.3 Exclusion Criteria

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

1) Previous treatment with at least 2 courses of decitabine (all stages) or azacitidine (Dose Confirmation Stage).
2) Known or suspected hypersensitivity to decitabine or the components of E7727.

3) Treated with any investigational drug or therapy within 2 weeks of study treatment, or 5 half-lives, whichever is longer, before the protocol-defined first dose of study treatment, or ongoing clinically significant adverse events from previous treatment with investigational drug or therapy.
4) Poor medical risk because of other conditions such as uncontrolled systemic diseases or uncontrolled active infections.
5) Diagnosis of AML with bone marrow or peripheral blast count ≥20% or other hematological malignancies.
6) Life-threatening illness, medical condition or organ system dysfunction, 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 oral decitabine + E7727, or compromise the integrity of the study outcomes.
7) Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, non-metastatic prostate cancer with normal prostate-specific antigen (PSA), or other cancer from which the subject has been disease free for at least 3 years.
8) Known history of human immunodeficiency virus (HIV) or if known seropositive for hepatitis C virus (HCV) or hepatitis B virus (HBV).
9) Active uncontrolled gastric or duodenal ulcer.

5.4 Withdrawal of Subjects

Subjects can withdraw from study treatment and continue study follow-up or withdraw from the study, as described below.

5.4.1 Withdrawal from Study Treatment

Subjects may withdraw from study treatment but still continue study follow-up procedures. Investigators are encouraged to assess all subjects according to the study protocol even after withdrawal from study treatment.

- Investigators can withdraw subjects from study treatment in case of unacceptable toxicity, non-compliance, unequivocal disease progression with clinical deterioration or a need to administer other anticancer treatment, or if it is determined by the investigator that it is in the subject's best interest.
- Astex Pharmaceuticals may require that a subject is withdrawn from treatment for safety reasons or for noncompliance.

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

It is important to obtain follow-up information on any subject withdrawn prematurely from study treatment. Every effort must be made to undertake protocol-specified follow-up procedures. Refer to Section 5.4.3 for specific assessments.

5.4.2 Withdrawal from the Study

Subjects may withdraw from the study at any time. It is important to obtain follow-up information, according to standard medical practice, on any subject withdrawn prematurely from the study. Every effort must be made to undertake at least standard assessments that are critical for efficacy or safety evaluation, such as Disease Progression (if the subject did not withdraw because of disease progression), Survival information, and Safety data. Refer to Section 5.4.3.

5.4.3 Follow-up Procedures after Withdrawal (from Treatment and/or the Study)

Section 10.0 describes follow-up for AEs. At minimum, subjects should be followed up for safety until 30 days after the last dose of study treatment (see Section 10.2). If at all possible, for all cases, subjects should undergo all end-of-study assessments (Treatment Termination visit and 30-day Follow-up visit; see Section 9.0).

For subjects willing to continue study follow-up procedures, the investigator should review the follow-up procedures with the subject, including the number of visits, the specific procedures to be done, and the total length of the follow-up period. The investigator must also ensure the subject understands that his or her medical records will continue to be available for the follow-up period as described in the approved ICF for the entire study period.

5.4.4 Replacement of Subjects

Enrollment of subjects for each cohort and stage of the study will continue until the required number of evaluable subjects for that cohort and stage is reached. The evaluable subject criteria are described in Section 11.1. Astex Pharmaceuticals may stop the study at any time. In this event, the Sponsor will make reasonable efforts to ensure subjects are transitioned off study in an orderly manner.

6.0 ENROLLMENT, RANDOMIZATION, AND BLINDING PROCEDURES

6.1 Enrollment

Subjects who meet the entry criteria will be enrolled/randomized into the study. Instructions regarding the enrollment process will be provided to the study centers in a separate document.

Subject identification (ID) numbers will consist of 6 digits. The first 3 digits will reflect the site number, followed by a 3-digit individual number within the site. The ID will be used to identify the subject throughout the study including the screening period and will be entered on all study documents.

6.2 Randomization

Randomization will occur in the Dose Confirmation Stage and the FDC Stage. In the Dose Confirmation Stage, subjects will be randomized in a 1:1 ratio to one of the two treatment sequences as described below:

- Oral decitabine + E7727 daily×5 in Course 1 followed by IV decitabine daily×5 in Course 2, or
- IV decitabine daily×5 in Course 1 followed by oral decitabine + E7727 daily×5 in Course 2.

In the FDC Stage, subjects will be randomized in a 1:1 ratio to receive one of the following treatment sequences:

- FDC tablet daily ×5 in Course 1 followed by IV decitabine daily ×5 in Course 2, or
- IV decitabine daily ×5 in Course 1 followed by the FDC tablet daily ×5 in Course 2.

Randomization will be stratified by the IPSS risk levels (lower risk of IPSS intermediate-1 versus higher risk of IPSS intermediate-2 and high-risk). Subjects with CMML will be randomized in the IPSS-2/high-risk stratum. Subjects should be treated as soon as possible after enrollment/randomization.

Treatment assignments for the individual subjects will be determined through a computer generated randomization scheme and accessed through the OmniComm TrialMaster system used for study data management. Instructions for access and use of the OmniComm TrialMaster system for randomization will be provided to participating study centers in a separate document.

6.3 Blinding

This is an open-label study. There will be no blinding of treatment assignment.

7.0 STUDY TREATMENTS

In this FIH trial, study treatment includes the combination of oral decitabine + E7727, the two separate IMPs administered concomitantly and given separately at designated time points, and also IV decitabine. Subjects will receive study treatment at the study center in the first course of treatment at all stages of the study, in the first 2 courses at Dose Confirmation Stage; and whenever PK sampling is required. At other visits, subjects may self-administer the IMPs at home. Astex Pharmaceuticals, Inc. will provide each study center with guidance to be provided to subjects for at-home dosing and drug storage.

7.1 Investigational Medicinal Products (IMPs)

7.1.1 Drug Form and Labeling

E7727 20 mg, decitabine 20 mg, and if needed decitabine 5 mg will be supplied separately in individual unit dosage forms, each as a hard gelatin capsule of specific color.

E7727 20 mg is available in a white opaque size 4 capsule packed in 30 count in a 30 cc white opaque HDPE bottle with a child resistant closure. Inactive ingredients present in the capsule are microcrystalline cellulose, hypromellose, and talc.

Decitabine 20 mg is available in a Swedish orange size 4 capsule packed in 30 count in a 30 cc white opaque HDPE bottle with a child resistant closure. Inactive ingredients present in the capsule are inert sugar spheres, hypromellose, and talc.

Decitabine 5 mg will be made available if needed in a light blue size 4 capsule packed in 30 count in a 30 cc white opaque HDPE bottle with a child resistant closure. Inactive ingredients present in the capsule are inert sugar spheres, hypromellose, and talc.

The FDC drug form of ASTX727 is a film-coated, oval, white, immediate-release tablet containing the combination of E7727 (100 mg) and decitabine (35 mg) for oral administration. The tablets will be packed in 5 count in an opaque HDPE bottle with a child resistant closure.

7.1.2 Storage

The IV decitabine drug product is sourced from commercial supplies and should be stored according to institutional policy and the manufacturer's label.

E7727 20 mg, decitabine 20 mg, and decitabine 5 mg, should be stored at 2°C to 8°C in a secure, locked facility at the study center and accessible only to authorized study personnel. Should E7727 and decitabine capsules be dispensed for outpatient administration, they should be dispensed by the study pharmacist according to institutional policy and in accordance with the Sponsor’s requirements.

The FDC tablet should be stored at 2°C to 8°C (36°F to 46°F) according to institutional policy and the Sponsor’s requirements.

7.1.3 Product Reconciliation

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

7.1.4 Study Treatment Administration

Subjects will be required to fast for 4 hours on days when receiving oral IMP. Fasting (no food, milk or alcohol) begins at least 2 hours prior to and ends 2 hours post-dose. Subjects will take oral

IMP(s) with 240 mL (8 fluid oz) of water. Clear liquids such as water, black coffee, tea, or fruit juice may be allowed as desired together with other concomitant medication that is needed to be given to the subject. Subjects should take the IMPs simultaneously (ie, E7727 followed immediately by oral decitabine). The IMPs should be taken at the same time of day (±1 hour) on each dosing day. If the subject vomits after oral dosing on one or more days, the dose of that day will not be re-administered, but vomiting should be recorded as an adverse event on the Case Report Form.

7.1.5 Missed Doses

It is important for subjects not to miss a dose, as PK assessments will be affected. Subjects should take the IMPs simultaneously (ie, E7727 followed immediately by oral decitabine) and at the same time of day (± 1 hr) on each dosing day during courses that include PK assessments. If a subject takes the IMPs outside the 1-hr window during a week with PK assessments, the subject should be instructed to notify the investigator immediately. If a dose is missed in subsequent courses, 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 scheduled time. Subjects should complete all 5 daily doses; if a dose is missed, the dosing period will extend to 6 days.

7.2 Active Comparator or Placebo

IV decitabine at 20 mg/m^2 will be the activate comparator as described. Decitabine is approved for IV infusion in the US and will be sourced locally at the US study centers. Decitabine IV will be provided by the sponsor as an IMP in Canada, as the product is not currently approved in Canada. Currently, the most commonly used regimen for treatment of MDS is 20 mg/m^2, 1-hour intravenous infusion for 5 daily administrations (Days 1-5) in a 28-day treatment course; this will be the comparator regimen in this study.

Refer to current decitabine label for storage and administration guidance.

7.3 Guidelines for Adjusting or Withholding Study Treatment

The algorithm describing dose escalation guidelines between cohorts in the Dose Escalation Stage is presented in Section 4.1.1, Figure 2. The actual decision to escalate or de-escalate and the actual dose levels will be determined by the DSRC based on PK and safety data (Section 4.4). Following the first course of treatment, the investigator should try to the best of his/her ability to assess whether an adverse event is related to study treatment. If the adverse event is judged to be related to study treatment and if it in the opinion of the investigator it requires dose adjustment, dosing delay and/or dose reduction may be recommended in subsequent treatment courses according to the following guidelines:

If the subject is still receiving treatment as part of the 5-day regimen, subsequent treatment days (Days 2-5) will be withheld if the subject develops any DLT as defined in Section 4.5, and the skipped doses will be missed. Dosing will also be withheld on Day 1 of any subsequent treatment

courses if the subject still has a DLT or other drug-related clinically significant toxicity that has not resolved to baseline or Grade 1 or have become ineligible by the protocol entry criteria (Section 5.0). Dosing may restart once the subject becomes eligible again and the DLT or other drug-related toxicity has resolved to either baseline or ≤Grade 1. If dosing is delayed by more than 4 weeks beyond Day 28, then the subject will be withdrawn from treatment unless it is judged by the Investigator to be in the subject's best interest to continue based on clinical benefit. If the subject has a DLT and it has resolved, he or she may be redosed for subsequent courses only at the next lower dose level of either E7727 or decitabine, if feasible.

In the Dose Confirmation Stage and the FDC Stage, investigators should attempt to give the full intended dose for at least 2 courses (Course 1 and Course 2) to be able to compare PK data as long as it is safe to do so. In all stages of the study, it is recommended to administer at least 6 courses of treatment to fully assess efficacy, unless unequivocal progression necessitating intervening therapy or unacceptable toxicity that is not manageable by dose reduction/delay or supportive treatment occurs. In the FDC Stage, dose reduction should begin by reducing treatment days to 4 days from 5. If further dose reduction is necessary, treatment days may be reduced to 3 days. It is recommended that dose reductions are done in consultation with the Astex medical monitor.

For subjects transitioning from the Dose Escalation Stage or Dose Confirmation Stage to the FDC Stage, any ongoing or future dose reductions should follow the FDC dose reduction recommendations through reduction of number of dosing days per cycle (ie, 4 or 3 days of FDC dosing rather than 5 days) as opposed to reductions of the daily dose, based on prior tolerance and safety data.

Additional delay or dose reduction may be applied based on investigator's judgment in consultation with the Astex medical monitor.

7.4 Concomitant Treatment

Record on the concomitant medication eCRF all treatments a subject receives, including supportive or palliative treatment (see below) whether prescription or over the counter (OTC), vitamin and mineral supplements, herbs, and medications taken for procedures (eg, biopsy). Also record antacids, proton pump inhibitors, H_2 antagonists (these should not be taken ±4 hours of administration of oral decitabine + E7727). Data will be collected on the start and stop dates as well as the indication for use in addition to the name, start and stop dates.

7.4.1 Supportive or Other Treatments

The investigator will be permitted 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. Should the subject vomit after any oral administration of study treatment, the dose(s) should not be re-administered on that day.

All supportive treatment including units of blood and platelet transfusions must be recorded on the eCRFs. 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, and blood culture. Subjects with febrile neutropenia or suspected sepsis on the basis of the physical examination are to be hospitalized for appropriate broad spectrum antibiotic coverage, consistent with local pathogen sensitivities.

Hematopoietic growth factors will not be routinely used. However, its use is permitted in case of a life-threatening septic event at the discretion of the treating physician. Erythropoietin and/or Neupogen can be used after Course 1 in the Dose Escalation Stage, after Course 1 and 2 in the Dose Confirmation Stage. Use of these agents should be guided by accepted practice or institutional guidelines.

7.4.2 Prohibited Medications

Prohibited concomitant therapies while on study are as follows: radiation therapy, chemotherapy, immunotherapy, or any experimental therapy. See Section 7.4 for additional information. Other nucleosides or drugs that are metabolized by CDA (Section 8.1) are also prohibited during the study when E7727 is being administered.

7.5 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) to Astex on the SAE form within 24 hours (see Section 10.3). Treat any AE (including SAE) based on standard care for the specific signs and symptoms. As this is the FIH study of oral decitabine + E7727, no data are available regarding the overdosage of oral decitabine + E7727. Based on the clinical experience of decitabine, an overdosage of oral decitabine + E7727 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 oral decitabine + E7727 or the FDC drug form.

8.0 RISKS/PRECAUTIONS

Please refer to the IB for ASTX727 and the IV decitabine prescribing information. As with any IMP, subjects may experience reactions or complications that are unknown, and therefore unpredictable.

8.1 Drug-Drug Interactions

The primary PD effect of E7727 is the inhibition of CDA, which is anticipated to enhance the oral bioavailability of decitabine. Hence, 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). As new agents may come to market during the trial, confer with the sponsor's medical monitor if questions arise.

Neither E7727 nor decitabine are expected to produce CYP-mediated drug-drug interactions, as these agents have shown no potential to inhibit or induce human CYP enzymes in vitro.

8.2 Genotoxicity

Decitabine is shown to be genotoxic, which could cause fetal harm. It is unknown whether E7727 can cause fetal harm. Therefore, subjects with reproductive potential must use methods of contraception during the study (as described in Section 5.1) and for 60 days after the last dose of decitabine. 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 decitabine immediately. Pregnancy in a female subject or a male subject's partner must be reported using Pregnancy Forms I and II.

9.0 STUDY ASSESSMENTS AND PROCEDURES

9.1 Efficacy Assessments

Efficacy assessments (via bone marrow aspirate or biopsy and peripheral blood count) will be based on the IWG 2006 MDS Response Criteria for MDS. A bone marrow aspirate/biopsy will be performed at Screening (within 21 days before first study treatment) and then within 7 days before Day 1 of every other course (Courses 3, 5, up to 7), then at the investigator's discretion to assess duration of response in responding subjects.

9.2 Pharmacokinetic/Pharmacodynamic/Biomarker Assessments

9.2.1 Pharmacokinetics (PK)

PK assessments will be based on AUC, C_{max}, C_{min}, and other PK parameters of decitabine, E7727, E7727-epimer, and cytidine levels. CDA activity will be measured at baseline from the predose sample in Course 1. The blood volume required per sample is 3 mL. Sampling should take place within ±10% of the scheduled time point, not to exceed ±1 hour at the 24-hour time point. Additional information regarding sample collection, processing, etc., will be provided in the laboratory manual. Also see Appendix 2.

9.2.1.1 Dose Escalation Stage, Course 1

PK assessments will be done at the following time points in Course 1:

- Day -3 (±2 days): 0 (pre-dose), 0.25, 0.5, 1, 1.5, 2, 3, 4 and 6 hours after dosing.

- Day 1: 0 (pre-dose), 0.25, 0.5, 1 (immediately before end of infusion), 1.083 (1 hour 5 min; 5 min after end of infusion), then 1.5, 2, 3, 4 and 6 hours from start of infusion.
- Day 2: 0 (predose), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 24 hours after dosing (Day 2, 24-hour sample is the pre-dose sample of Day 3).
- Day 3: pre-dose only (this is Day 2, 24-hour sample).
- Day 4: pre-dose only.
- Day 5: 0 (predose), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8 hours.

9.2.1.2 Dose Escalation Stage, Course 2

- Day -3 (±2 days): 0 (pre-dose), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 24 hours after dosing (if 24-hour sample is on Day 1 then obtain sample before the E7727 dose if E7727 dose administered one day before Day 1).

9.2.1.3 Dose Confirmation Stage

PK assessments from the Dose Escalation Stage showed that decitabine blood levels on the first day of oral dosing (Day 2) were lower than on Day 5. This necessitates additional assessments of decitabine levels over the 5 days of oral dosing to estimate the AUC over the entire 5-day cycle. PK assessments will be done at the following time points according to the randomization assignment in Courses 1 and 2.

When receiving IV decitabine:

- Day 1: 0 (pre-dose), 0.25, 0.5, 1 (immediately before end of infusion), then 1.083 (1 hour 5 min; 5 min after end of infusion), 1.5, 2, 3, 4 and 6 hours from the start of infusion.

When receiving oral decitabine + E7727:

- Day 1: 0 (pre-dose), and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 24 hours after dosing (Day 1, 24-hour sample is the pre-dose sample of Day 2).
- Day 2: 0 (pre-dose), and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 24 hours after dosing (Day 2, 24-hour sample is the pre-dose sample of Day 3).
- Day 3: 0 (pre-dose), 0.5, 1, and 2 hours after dosing.
- Day 4: 0 (pre-dose), 0.5, 1, and 3 hours after dosing.
- Day 5: 0 (pre-dose), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8 hours after dosing.

After complete PK data from the first 12-24 subjects in the Dose Confirmation Stage are evaluated, PK assessments may be further modified to reduce the number of required collections.

9.2.1.4 Fixed-Dose Combination Stage

When receiving the FDC tablet:

- Day 1: 0 (pre-dose), and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 24 hours after dosing (Day 1, 24-hour sample is the pre-dose sample of Day 2).
- Day 2: 0 (pre-dose).
- Day 3: 0 (pre-dose).
- Day 4: 0 (pre-dose).
- Day 5: 0 (pre-dose), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8 hours after dosing.

When receiving IV decitabine:

- Day 1: 0 (pre-dose), 0.25, 0.5, 1 (immediately before end of infusion), then 1.083 (1 hour 5 min; 5 min after end of infusion), 1.5, 2, 3, 4 and 6 hours from the start of infusion.

9.2.2 Pharmacodynamics

PD assessments will be based on cytidine levels and LINE-1 DNA methylation.

9.2.2.1 Dose Escalation Stage

LINE-1 DNA methylation will be assessed at Screening and at the following time points in Course 1:

- Day 1 (pre-dose), and at Days 8, 15, 22.

LINE-1 DNA methylation will be assessed at the following time points in Course 2:

- Day 1 (pre-dose), Days 8, 15, 22, and 29 (ie, before Course 3).

9.2.2.2 Dose Confirmation Stage

LINE-1 DNA methylation will be assessed at Screening and at the following time points in Courses 1 and 2 only in Dose Confirmation Stage:

- Day 1 (pre-dose), and at Days 8, 15, 22, and 29 (ie, before the subsequent course).

9.2.2.3 Fixed-Dose Combination Stage

LINE-1 DNA methylation will be assessed at Screening and at the following time points in Courses 1 and 2 in the FDC stage:

- Day 1 (pre-dose), and at Days 8, 15, 22, and 29 (ie, before Course 3, Day 1).

9.3 Safety Assessments

Safety will be assessed by subject reported and investigator observed AEs, along with physical examination, ECGs and clinical laboratory tests (hematology, chemistries, and urinalysis). AEs will be monitored through the 30-Day (+5 day) Follow-up Visit.

9.4 Study Procedures

9.4.1 Schedule of Events

Table 3 shows the dosing schedule by Stage and Course. Table 4 presents the complete schedule of events for all study stages, with details following in text. Additional information on the study procedures is provided in the study procedures manual. A detailed dosing schedule by stage and course is in Table 3. Time points for PK assessments are in Appendix 2. At any time in the study, one or more assessments may be eliminated at the recommendation of the DSRC if no longer needed to assess safety, PK, or PD of the study treatment.

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

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

Table 3: Dosing Schedule by Stage and Course

Course (28 Days)	**1**			**2**		**≥3**
Course Day	-3 (±2)	1	2-5	-3 (±2)	1-5	1-5
Dose Escalation Stage						
Single dose decitabine (oral)	x					
Single dose E7727				x		
IV decitabine (20 mg/m^2)		x				
Oral decitabine + E7727			x		x	x
Dose Confirmation Stage						
If randomized to IV decitabine in Course 1, then:						
IV decitabine (20 mg/m^2)		x	x			
Oral decitabine + E7727					x	x
If randomized to oral decitabine + E7727 in Course 1, then:						
Oral decitabine + E7727		x	x			x
IV decitabine (20 mg/m^2)					x	
Fixed-Dose Combination Stage						
If randomized to IV decitabine in Course 1, then:						
IV decitabine (20 mg/m^2)		x	x			
FDC tablet					x	x
If randomized to the FDC tablet in Course 1, then:						
FDC tablet		x	x			x
IV decitabine (20 mg/m^2)					x	
Transition to FDC Tablet		x	x		x	x

NOTE: On days when subjects are administered E7727 + oral decitabine, subjects should take the IMPs simultaneously (ie, E7727 followed immediately by oral decitabine). The IMPs should be taken at the same time of day (±1 hour) on each dosing day, in at least the first 2 courses of treatment.

Table 4: Schedule of Events

Course (28 Days)		**1**						**2**						**≥3**[a]					**Tx Term**[b]	**30-Day FU**[c]	**Survival**
Course Day		-3[d] (±2)	1	2-5	8 (±1)	15 (±2)	22 (±2)	-3[d] (±2)	1	2-5	8 (±1)	15 (±2)	22 (±2)	1	2-5	8 (±2)	15 (±2)	22 (±2)			
Study Treatment Administration (see Table 3)		x	x	x				x	x	x				x	x						
PROCEDURES[a]	**Screening**[e]																				
Informed consent	x																				
Medical history[f]	x																				
Investigator's confirmation of eligibility	x																				
Physical exam or (symptom-directed PE)[g]	x	x	x	(x)	(x)	(x)	(x)	x	x	(x)	(x)	(x)	(x)	x					x	(x)	
Height	x																				
Weight/BSA calculation[h]	x		x						x										x		
Vital signs[i]	x	x	x	(x)				x	x	(x)				x					x		
ECOG status[j]	x	x	x					x	x					x					x	x	
12-lead ECG[k]	x	x	x					x	x					x					x		
ECHO or MUGA[l]	x																				
Concomitant medications/AEs[m]	x	x	x	(x)	x	x	x	x	x	(x)	x	x	x	x					x	x	
Transfusion requirements[n]	x	x	x	(x)	x	x	x	x	x	(x)	x	x	x	x					x		
LABORATORY ASSESSMENTS[a]																					
Hematology[o]	x	x	x		x	x	x	x	x		x	x	x	x					x		
Chemistry[p]	x	x	x					x	x					x					x		
Urinalysis[q]	x	x	x																x		
Serum or urine pregnancy test[r]	x																		x		
IPSS Risk Category[s]	x																				
LINE-1 DNA methylation; [redacted]	x		x		x	x	x		x		x	x	x	x							

Table 4: Schedule of Events (Cont'd)

Course (28 Days)		1						2						≥3[a]					Tx Term[b]	30-Day FU[c]	Survival
Course Day		-3[d] (±2)	1	2-5	8 (±1)	15 (±2)	22 (±2)	-3[d] (±2)	1	2-5	8 (±1)	15 (±2)	22 (±2)	1	2-5	8 (±2)	15 (±2)	22 (±2)			
PK – Dose Escalation Stage[u]		x	x	x				x	x												
PK – Dose Confirmation Stage[u]			x	x					x	x											
PK – FDC Stage[u]			x	x					x	x											
Response assessment[v]			x					x						x						x	
Bone marrow aspirate/biopsy[w]	x													x						x	
Conversion to AML[x]																					x

a. The visit schedule and assessments are at the investigator's discretion after Course 6, with the exception of adverse event and dosing information, which will still be collected. Continue to collect efficacy assessments, response assessment and survival data according to the protocol until disease progression (for response assessment) or death (for survival assessment).

b. Perform Treatment Termination Visit procedures when a subject withdraws from further study treatment regardless of whether the subject withdrew from the whole study or not. The visit may occur at any time after the last study treatment and before the 30-day Follow-up visit. If the Treatment Termination Visit occurs close to the 30-day Follow-up visit, the 2 visits may be combined.

c. 30-Day Follow-up Visit must occur 30 (+5) days after the last dose of study treatment or within 3 days before starting new treatment. For 30-Day Follow-up via telephone, assess as much as possible but at a minimum assess AEs.

d. Day -3 (±2 days): Applies only to Dose Escalation Stage Course 1 and Course 2.

e. Screening: Must occur within 14 days before the first dose of decitabine, except for bone marrow biopsy/aspirate (may occur within 21 days before first dose of study treatment), and ECHO/MUGA (may occur within 28 days before first dose of study treatment).

f. Medical history: Includes demographics and disease history at Screening.

g. Physical Exam (PE): A complete PE performed at Screening per the institutional standard practice includes examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system and genitourinary system (if applicable). After Screening, symptom-directed PE (indicated by (x)) will be done pre-dose on Days 2-5 only if the subject is visiting the clinic for study purposes, and at all subsequent visits at the investigator's discretion. For Dose Escalation Stage subjects who had full PE performed at Screening within 4 days of Course 1 Day -3, it is not necessary to repeat the full PE on Day 1 during Course 1; a symptom-directed PE on Day 1 can be done instead. For Dose Escalation Stage subjects who had a full PE at Day -3 (±2) in Course 1 and Course 2, it is not necessary to repeat the full PE on Day 1 during these courses; a symptom-directed PE on Day 1 can be done instead. For Dose Confirmation Stage or Fixed-Dose Combination Stage, subjects who had full PE performed at Screening within 4 days of Course 1 Day 1, it is not necessary to repeat the full PE on Day 1 during Course 1; a symptom-directed PE on Day 1 can be done instead.

h. BSA calculation applies only to the Screening and the first visit of the course in which the subject is receiving IV decitabine (20 mg/m^2) or whenever dosing is given per surface area. Day 1, Dose Escalation Stage; Day 1, Dose Confirmation Stage (Course 1 or 2 according to randomization). Use actual body weights only for BSA calculations. BSA does not need to be performed at the Termination visit.

i. Vital signs: Include resting systolic/diastolic blood pressure, resting respiration rate, resting heart rate, and body temperature. Assess after the subject has rested in the sitting position for at least 3 minutes. On Days 2-5 in Course 1 and Course 2, perform vital signs only if the subject is visiting the clinic for study procedures (eg, administration of IV decitabine).

j. ECOG status: Complete at Screening and predose as indicated in above table. In Course 1, if assessed on Day -3 (±2) in Dose Escalation Stage or Screening (± 4 days) in the Dose Confirmation Stage or Fixed-Dose Combination Stage, it is not necessary to repeat on Day 1.

k. 12-Lead ECG (single tracing only, unless clinically significant abnormality for which triplicate ECG is preferred for confirmation, eg, QTc >500 msec): Obtain predose as indicated in above table. In Course 1, if assessed on Day -3 (±2) in Dose Escalation Stage or Screening (± 4 days) in the Dose Confirmation Stage or Fixed-Dose Confirmation Stage, it is not necessary to repeat on Day 1. Either the Bazett's or Fridericia's formula may be used to calculate the QTc interval but must be consistently used throughout the study. Course ≥3: Day 1 only.

l. ECHO/MUGA: May be done within 28 days of first dose of study treatment.

m. Concomitant medications/Adverse events: Collect all AEs on indicated study days through the 30-Day Follow-up Visit. Collect all concomitant treatments through the termination visit and then only those used to treat AEs through the 30-Day Follow-up Visit. After 30-day follow up, collect only SAEs that are considered related to the study treatment.

n. Transfusion requirements: Assess PRBC and platelet transfusions 8 weeks prior to study entry and then at on indicated study days.

o. Hematology: Must include complete blood count with manual differential and platelet counts. In Course 1, Day -3 (±2) in Dose Escalation Stage and Course 1, Day 1 in the Dose Confirmation Stage or Fixed-Dose Combination Stage, hematology evaluations do not need to be repeated if Screening tests are within 4 days of first dose of study treatment. In Course 2, Day 1 in the Dose Escalation Stage, hematology evaluations do not need to be repeated if Course 2 Day -3 (±2) is performed within 4 days of Course 2, Day 1 dose. Additional laboratory assessments may be done at the investigator's discretion for clinical interventions.

p. Chemistry: 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 (Section 5.2). Course 1, Day -3 (±2) in the Dose Escalation Stage and Course 1, Day 1 in the Dose Confirmation Stage or Fixed-Dose Combination Stage, chemistry evaluations do not need to be repeated if screening tests are within 4 days of first dose of study treatment. In Course 2, Day 1 in the Dose Escalation Stage, chemistry evaluations do not need to be repeated if Course 2 Day -3 (±2) is performed within 4 days of Course 2, Day 1 dose. For Course 1, Day -3 (±2) in Dose Escalation Stage and Course 1, Day 1 in the Dose Confirmation Stage or Fixed-Dose Confirmation Stage, all chemistry evaluations must meet study entry criteria before dosing. Additional laboratory assessments may be done at the investigator's discretion for clinical interventions.

q. Urinalysis: Dipstick only (microscopic analysis required only to follow up abnormal findings or if dipstick not performed). (See Table 5.) Includes microscopic examination. Course 1, Day -3 (±2), Dose Escalation Stage only. Course 1, Day 1 – Dose Confirmation Stage or Fixed-Dose Combination Stage. Urinalysis evaluations do not need to be repeated if screening tests are within 4 days before first dose of study treatment.

r. Pregnancy test: Serum or urine; only for women of child-bearing potential.

s. IPSS Risk Category: Int-1: 0.5–1; - Int-2: 1.5-2; High risk: ≥2.5.

t. LINE-1 DNA methylation: LINE-1 DNA at Screening and pre-dose in Courses 1, 2, and 3 only, and on designated days of Course 1 and 2 only (see Sections 9.2.2, 9.4.3.2, 9.4.3.4, 9.4.4, 9.4.5, 9.4.5.1). Information regarding sample collection storage is provided in the Study Laboratory Manual.

u. PK: see Appendix 2.

v. Response assessment: Refer to Table 7 for the appropriate disease assessment.

w. Bone marrow aspirate or biopsy: The screening bone marrow aspirate or biopsy must occur within 21 days of the first dose of study treatment. Bone marrow aspirate must be done to verify first CR, PR, mCR immediately when peripheral blood counts suggest a response, and within 7 days before the start of each odd course (Courses 3, 5, up to 7), as long as the subject continues to be responding, then according to local standard practice. Otherwise, this may be done at the investigator's discretion. 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. 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, Other. An anonymized report of all bone marrow testing results will be recorded on the Case Report Form. A portion of bone marrow aspirates will be used for assessing [redacted]. 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.

x. Conversion to AML: Follow all subjects for survival who have stopped study treatment. Contact each subject at least every 3 months until death or withdrawal of consent. This assessment may be conducted by telephone.

9.4.2 Screening and Baseline Procedures

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

Within 14 days before treatment administration (unless otherwise specified), perform the following study procedures and tests:

- Written informed consent. The ICF must be signed and dated by the subjects before any study-specific samples are collected or study-specific procedures are initiated.
- Complete medical history, including demographics (date of birth, sex, race). Record disease history, including the date of initial diagnosis. Document concurrent medical signs and symptoms to establish baseline conditions.
- Investigator's confirmation of eligibility. Perform all necessary procedures and evaluations to document that the subject meets each eligibility criterion.
- Complete physical exam as per the institution standard practice including examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and genitourinary system (if applicable).
- Obtain height and weight/BSA calculation.
- Vital signs include resting (assessed after the subject has rested in a sitting position for at least 3 minutes) systolic/diastolic blood pressure, resting respiration rate, resting heart rate, and body temperature (vital signs).
- ECOG performance status (Appendix 3).
- 12-lead ECG – single tracing only (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, one formula but must be consistently used throughout the study. Course ≥3: Day 1 only.
- ECHO or MUGA; may be performed up to 28 days before study treatment.
- Record concomitant medications.
- Assess transfusion dependency status. See Section 9.6 for definitions of transfusion dependence and independence.
- Collect blood samples for hematology and serum chemistry, and urine sample for urinalysis (Table 5).
- 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.
- Assess IPSS, number of prior cancer treatments.
- Obtain whole blood sample for LINE-1 DNA methylation (all groups).

- Collect bone marrow aspirate or biopsy including bone marrow cytogenetics of 20 clones (may be performed up to 21 days before administration of study treatment). A portion of Screening bone marrow aspirates will be used for assessing [redacted].

Table 5: Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis	Pregnancy Test
-Complete blood count (CBC) -Manual differential -Platelet count	-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 described in Table 4.

9.4.3 Treatment and Follow-up Procedures

9.4.3.1 Course 1, Day -3 (±2) – Dose Escalation Stage Only

Complete the following assessments before dosing:

- Complete physical examination (PE) including weight/BSA (may be a symptom-directed PE if a full PE was completed within 4 days of this visit).
- Vital signs.
- ECOG performance status (Appendix 3; may be waived if completed within 4 days prior to visit).
- 12-lead ECG – single tracing only.
- Record concomitant medications /adverse events.
- Verify transfusion dependency status.
- Collect blood samples for hematology and serum chemistry, and urine sample for urinalysis (Table 5). (May be waived if completed within 4 days prior to the visit.)
- Obtain PK sample per Appendix 2.

- Administer oral decitabine at assigned cohort dose level after a fast of at least 2 hours; administer with 240 mL (8 fluid ounces) of water. No food, milk or alcohol should be allowed for at least 2 hours post-dose. Clear liquids such as water, black coffee, tea, or fruit juice may be allowed as desired. Ensure subject is clinically stable prior to discharging home after all PK samples have been obtained.

9.4.3.2 Course 1, Day 1 – All Stages

Complete the following assessments before dosing (see Table 6):

- Physical examination: see Table 6.
- Weight/BSA calculation: see Table 6.
- Vital signs.
- ECOG Performance Status (Appendix 3; may be waived if completed within 4 days prior to visit).
- 12-lead ECG – single tracing only (may be waived if completed within 4 days prior to visit).
- Record concomitant medications and adverse events.
- Record any transfusion requirements since last visit (for the Dose Confirmation Stage, assess transfusion dependency status).
- Collect blood samples for hematology and serum chemistry, and urine sample for urinalysis (Table 5). (May be waived if completed within 4 days prior to the visit.)
- Obtain whole blood sample for LINE-1 DNA methylation.
- Obtain PK samples per Appendix 2.
- Assess response.

Table 6: Day 1 Assessments – All Stages

Assessment	Dose Escalation Stage	Dose Confirmation Stage	Fixed-Dose Combination Stage
Physical Examination[a]	Symptom-directed Exam	Complete Exam	Complete Exam
Weight/BSA calculation	x/x	x/x[b]	x/x[b]
LINE-1 demethylation	x	x	x
Predose PK sample	x	x	x

[a] Symptom-directed PE for subjects in the Dose Escalation Stage if completed at Day -3(± 2) visit or for subjects in Dose Confirmation Stage or FDC Stage if full PE completed at Screening visit within 4 days of this visit.

[b] When receiving IV decitabine (unless oral decitabine + E7727 requires Weight/BSA dose adjustment after PK review by DSRC).

Dosing and post-dosing procedures:

- Administer the study treatment:
  - Dose Escalation Stage: IV decitabine (20 mg/m^2) as a 1-hour infusion.
  - Dose Confirmation Stage: Either IV decitabine (20 mg/m^2) or oral decitabine + E7727 at assigned dose (based on randomization assignment).
  - FDC Stage: Either FDC tablet administered orally, or IV decitabine (20 mg/m^2) as a 1-hour infusion.

If administering oral decitabine + E7727, or the FDC tablet, administer after a fast of at least 2 hours, with 240 mL (8 fluid ounces) of water. No food, milk or alcohol should be allowed for at least 2 hours post-dose. Clear liquids such as water, black coffee, tea, or fruit juice may be allowed as desired.

- Obtain PK samples per Appendix 2.
- Record any new concomitant medications and adverse events.

9.4.3.3 Course 1, Days 2-5 – All Stages

On days the subject comes to the clinic for IV decitabine or PK assessments complete the following assessments before dosing:

- Symptom-directed physical examination.
- Vital signs.
- Record concomitant medications and adverse events (pre- and post-dosing).
- Record any transfusion requirements since last visit.
- Collect PK samples per Appendix 2 (pre- and post-dosing).

Dosing and post-dosing procedures:

- Administer the study treatment:
  - Dose Escalation Stage: oral decitabine + E7727 at assigned dose for cohort.

- Dose Confirmation Stage: Either IV decitabine (20 mg/m^2) or oral decitabine + E7727 at assigned dose (based on randomization assignment).
- FDC Stage: Either FDC tablet administered orally, or IV decitabine (20 mg/m^2) as a 1-hour infusion.

If administering oral decitabine + E7727, or the FDC tablet, administer after a fast of at least 2 hours, administer with 240 mL (8 fluid ounces) of water. No food, milk or alcohol should be allowed for at least 2 hours post-dose. Clear liquids such as water, black coffee, tea, or fruit juice may be allowed as desired.

- Record any new concomitant medications and adverse events.

9.4.3.4 Course 1, Days 8, 15, 22 – All Stages

Complete the following for all stages unless otherwise indicated:

- Symptom-directed physical examination.
- Record concomitant medications and adverse events.
- Record any transfusion requirements since last visit.
- Collect hematology samples (Table 5).
- Collect whole blood sample for LINE-1 DNA methylation.

9.4.3.5 Course 2, Day -3 (±2) – Dose Escalation Stage only

Complete the following predose:

- Complete physical examination (symptom directed only if subject is visiting the clinic for study procedures).
- Vital signs only if subject is visiting the clinic for study procedures.
- ECOG performance status (Appendix 3).
- 12-lead ECG – single tracing only.
- Record concomitant medications and adverse events (pre- and post-dosing).
- Record any transfusion requirements since last visit.
- Collect blood samples for hematology and chemistry samples (Table 6).
- Collect PK sample (see Appendix 2) (pre- and post-dosing).

Dosing and post-dosing procedures:

- Administer single oral dose of E7727 at assigned cohort dose level after a 2-hour fast with 240 mL (8 fluid ounces) of water. No food, milk or alcohol should be allowed for at least 2 hours post-dose. Liquids such as water, black coffee, tea, or fruit juice may be allowed as desired.
- Record any new concomitant medications and adverse events.

9.4.4 Course 2, Days 1-5 – All Stages

Complete the following predose:

- Complete physical examination on Day 1 (may be symptom-directed for Dose Escalation Stage subjects if completed at Day -3 [±2] visit) and symptom-directed physical examination on Days 2-5 only if subject is visiting the clinic for study procedures.
- Weight and BSA calculation (BSA calculation required on Day 1 in Dose Escalation Stage and for those receiving IV decitabine in Dose Confirmation Stage, Day 1 only).
- Vital signs: Days 2-5 only if subject is visiting the clinic for study procedures.
- EGOG performance status (Day 1 only).
- 12-lead ECG – single tracing only (Day 1 only).
- Record concomitant medications and adverse events (pre- and post-dosing).
- Record any transfusion requirements since last visit.
- Collect blood samples for hematology and serum chemistry on Day 1 only (Table 5).
- Obtain sample for LINE-1 DNA methylation (Day 1 only).
- Collect samples for PK assessment (see Appendix 2) (pre- and post-dosing).

Dosing and post-dosing procedures:

- Administer the study treatment:
  - Dose Escalation Stage: oral decitabine + E7727 at assigned dose.
  - Dose Confirmation Stage: Either IV decitabine (20 mg/m^2) or oral decitabine + E7727 at assigned dose (based on randomization assignment).
  - FDC Stage: Either FDC tablet administered orally, or IV decitabine (20 mg/m^2) as a 1-hour infusion.

If administering oral decitabine + E7727, or the FDC tablet, administer after a fast of at least 2 hours, administer with 240 mL (8 fluid ounces) of water. No food, milk or alcohol should be allowed for at least 2 hours post-dose. Clear liquids such as water, black coffee, tea, or fruit juice may be allowed as desired.

- Record any new concomitant medications and adverse events.

9.4.5 Course 2, Days 8, 15, and 22 – All Stages

Complete the following for all stages unless otherwise indicated:

- Symptom-directed physical examination.
- Record concomitant medications and adverse events.
- Record any transfusion requirements since last visit.
- Collect hematology samples (Table 5).
- Collect whole blood sample for LINE-1 DNA methylation.

9.4.5.1 Course ≥3, Days 1-5 – All Stages

All procedures are to be completed at all visits through Course 6. Beginning with Course 7 and later courses, all procedures are at the discretion of the investigator except for Adverse Event, dosing information, and response assessment. Data will be collected on all procedures completed.

Complete the following predose:

- Complete physical examination (Day 1 only).
- Vital signs (Day 1 only).
- EGOG performance status (Day 1 only).
- 12-lead ECG – single tracing only (Day 1 only).
- Record concomitant medications and adverse events (Day 1 only).
- Record any transfusion requirements since last visit (Day 1 only).
- Collect blood samples for hematology and chemistry (Day 1 only) (Table 5).
- Collect whole blood sample for LINE-1 DNA methylation (only Course 3 Day 1 predose)
- Assess response (obtain predose on Day 1 in every odd numbered course).
- Bone marrow aspirate or biopsy within 7 days before the start of Course 3, Course 5, and Course 7, as long as the subject continues to be responding; thereafter, according to a schedule that is standard practice at the study center. A portion of bone marrow aspirates will be used for assessing [redacted].

Dosing and post-dosing procedures:

- Administer oral decitabine + E7727 at assigned dose, or the FDC tablet, after a fast of at least 2 hours, administer with 240 mL (8 fluid ounces) of water. No food or milk should be allowed

for at least 2 hours post-dose. Clear liquids such as water, black coffee, tea, or fruit juice may be allowed as desired. No alcohol should be ingested throughout an entire treatment day.

- Record any new concomitant medications and adverse events.

9.4.5.2 Treatment Termination

Perform Treatment Termination Visit procedures when a subject withdraws from further study treatment regardless of whether the subject withdrew from the whole study or not. The visit may occur at any time after the last study treatment and before the 30-Day Follow-up Visit. If the Treatment Termination Visit occurs close to the 30-Day Follow-up Visit, the 2 visits may be combined. Complete the following upon subject termination:

- Complete physical examination, weight, vital signs, ECOG performance status, 12-lead ECG (single tracing only).
- Record concomitant medications and adverse events.
- Record any transfusion requirements since last visit.
- Collect blood samples for hematology and serum chemistry and urine sample for urinalysis (Table 5).
- Serum or urine pregnancy test: for women of child-bearing potential only.

9.4.5.3 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 treatment. The 30-day Follow-up Visit may be completed in person or by telephone. For 30-Day Follow-up via telephone, assess as much as possible but at a minimum assess AEs. If the 30-day Follow-up Visit occurs close to the Treatment Termination Visit, the 2 visits may be combined.

- Symptom-directed physical examination.
- ECOG performance status (Appendix 3).
- Assess concomitant medications and adverse events.
- Assess response (see Table 7).
- Perform bone marrow aspirate or biopsy.

9.4.5.4 Survival/Conversion to AML

Follow all subjects for survival who have stopped study treatment. Contact each subject every 3 months until death or withdrawal of consent. This assessment may be conducted by telephone.

9.5 Missed Evaluations

Evaluations should occur within the visit window specified by the protocol. If an evaluation is missed, reschedule and perform it as close as possible to the original date. If rescheduling becomes, in the investigator's opinion, medically unnecessary because the evaluation would occur too close to the next scheduled evaluation, it may be omitted.

9.6 Response Criteria

The response criteria for evaluation of MDS are based on the International Working Group criteria published by Cheson et al. (2006) and are shown in Table 7.

Table 7: IWG 2006 MDS Response Criteria

Complete Response (CR): the following for 4 weeks		
Peripheral: normal peripheral counts with persistent granulocyte count ≥ 1.0 x 10^9/L, platelet ≥ 100 x 10^9/L		
Marrow: normal bone marrow with persistent marrow blasts ≤ 5%; peripheral dysplasia will be noted		
Partial Response (PR): the following for 4 weeks		
Peripheral: normal peripheral counts with granulocyte count ≥ 1.0 x 10^9/L and platelet count ≥ 100 x 10^9/L		
Marrow: normal bone marrow and marrow blasts > 5% but were reduced by 50% or more		
Marrow Complete Response (mCR): the following 4 weeks		
Reduction of bone marrow blasts to ≤ 5% without normalization of peripheral counts		
Hematological Improvement (HI): lasts at least 8 weeks[a]		
Erythroid Response (HI-E):	Major Response:	hemoglobin increase ≥ 1.5 g/dL or RBC transfusion dependence
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
Neutrophil Response (HI-N):	Major Response:	granulocyte increase ≥ 100%, and by an absolute increase ≥0.5 X 10^9/L

[a] Abnormal baseline counts were the averages of at least two measurements over at least one week prior to therapy, not influenced by transfusions.

Transfusion dependence and independence will be defined by the transfusion requirements during the 8 weeks before study treatment start (Steensma et al 2009):

- Transfusion dependent anemia at baseline: documentation of 2 units or more PRBCs within 56 days of the first day of study treatment
- Post-treatment Transfusion independence : no blood transfusion of 2 or more units of PRBCs for 56 days or more after treatment

10.0 EVALUATION, RECORDING, AND REPORTING OF ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Event (AE)

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

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

10.1.2 Serious Adverse Events (SAEs)

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

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

Important medical events that may not result in death, be life-threatening or require hospitalization may be considered serious when, based on the appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE. Examples of such medical events are intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or development of drug dependency or drug abuse.

10.2 Adverse Event Reporting and Descriptions

Record new AEs from the start of study treatment until 30 days after the last dose of study treatment. Also record screening procedure-related AEs that occur before the start of study treatment.

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

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

For any change in laboratory results, vital signs, physical examination, radiologic exam or ECG measurements that arises after treatment, the investigator will decide if the finding or result is clinically significant and will determine if it is necessary to repeat the evaluation. If the investigator judges the finding or result as clinically significant, it must be recorded as an AE, and if applicable, reported as an SAE. Clinically significant laboratory findings include any laboratory result for which a therapeutic intervention is initiated to correct the abnormality; this excludes intervention to correct the abnormality as part of the disease state or disease progression.

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 v4.0 for grading the severity (intensity) of AEs. The CTCAE v4.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE v4.0, 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 (e.g., 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 (e.g., 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 (e.g., acute myocardial infarction in a young woman), • An aggregate analysis of specific events observed in a clinical study (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group that in a concurrent or historical control group.

Not Related (Not Suspected)	Adverse events that do not meet the definition above.

10.2.3 Pregnancy and Abortion

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

A subject must immediately inform the investigator if the subject or subject's partner becomes pregnant during the time between the first study-specific procedure and 60 days after the last dose of study treatment. Any female subjects receiving the study treatments who become pregnant must immediately discontinue study treatment. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

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

10.3 Reporting and Evaluation of Serious Adverse Events

10.3.1 Reporting Requirements for Serious Adverse Events (SAEs)

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

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

Astex Pharmaceuticals Drug Safety Contact Information	
PRIMARY CONTACT: Email:	[redacted]
North America Local Fax:	
North America Toll Free Fax:	
Other countries: Refer to the Astex Fax Cover Sheet for the Drug Safety Department. All safety fax numbers are listed there.	

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

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

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

10.4 Follow-up for Adverse Events

Follow all AEs and SAEs assessed as related to study treatment or study procedures 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, Inc. or its designee.

Data summaries and listings will be generated using SAS version 9.3 or higher (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 and spurious data. The clinical study report will describe deviations from the statistical analysis plan, if any.

11.1 Sample Size

11.1.1 Dose Escalation Stage

For this stage, no formal statistical tests of hypotheses are performed to calculate sample size. The Dose Escalation Stage follows a standard 3+3 design, with a cohort size of 3-12 evaluable subjects (and may be extended to 18 subjects to confirm the AUC range, if recommended by the DSRC). The enrollment of subjects in the Dose Escalation Stage will continue until the desired decitabine AUC level (AUC ratio of 0.90 to 1.10 of oral decitabine to IV decitabine) and safety are achieved, as described in Section 4.1.1. A subject is considered evaluable for the Dose Escalation Stage if all the criteria below are met:

- Complete Course 1 dosing regimen with sufficient PK data available.
- Safety assessment for the 28 days of Course 1.

11.1.2 Dose Confirmation Stage

At least 42 evaluable subjects are planned for enrollment into the Dose Confirmation Stage.

Forty-two evaluable subjects with an IPSS risk level of intermediate-1, intermediate-2, or high risk are needed to assess decitabine AUC (estimated from 5 days of dosing) and LINE-1 demethylation, using a standard 2 x 2 cross-over design, between IV decitabine 20 mg/m^2 daily×5 and the recommended doses of oral decitabine + E7727 as determined in the Dose Escalation Stage. Evaluable subjects for this assessment of decitabine and LINE-1 DNA demethylation are those who meet all the following criteria:

- Complete the dosing regimens in Courses 1 and 2 with sufficient PK data available.
- Have at least one bone marrow aspirate/biopsy after Course 2.

In an equivalence test of the mean decitabine AUCs of oral decitabine + E7727 (estimated from 5 days of dosing) compared with IV decitabine using two one-sided tests on data from a 2 x 2 cross-over design, a sample size of 42 achieves 86% power at a 10% significance level when the true ratio of the means is 1.0, the coefficient of variation on the original, unlogged scale is 0.50 which was estimated from a previous study described in the Dacogen Prescribing Information (2014), and the equivalence limits of the mean ratio are 0.75 and 1.33.

This same sample size of 42 in the same 2 x 2 cross-over design achieves 80% power to detect the non-inferiority, with respect to the mean maximum %LINE-1 demethylation from baseline, of oral decitabine + E7727 compared with IV decitabine using a one-sided t-test when the margin of non-inferiority is -0.05, the true mean difference is 0, the standard deviation (SD) is 0.15 and the significance level is 0.10. The SD of the paired differences of 0.15 was estimated from a previous study.

11.1.3 Fixed-Dose Combination Stage

Subjects in a standard 2 x 2 crossover design are considered evaluable for equivalence analysis if those subjects complete treatment in Courses 1 and 2 with sufficient PK data. A total of 18-24 evaluable subjects included in the 2 one-sided equivalence tests for mean oral decitabine AUC compared with mean IV decitabine AUC will provide 75%-88% power at a 10% significance level when the true ratio of means is 1.0, the coefficient of variation under an unlogged scale is 0.55, and the equivalence limits for the ratio of means are 0.65 and 1.539.

The 18-24 subjects who complete Courses 1 and 2 with sufficient LINE-1 data in the same 2 x 2 crossover design will provide 78%-86% power to detect non-inferiority, with respect to the mean maximum %LINE-1 demethylation from baseline, of the ASTX727 FDC tablet compared with IV

decitabine using a one-sided t-test when the margin of non-inferiority is 0.075, the true mean difference is 0, the standard deviation (SD) is 0.15 and the significance level is 0.10.

11.2 Data Sets to be Analyzed

11.2.1 All Enrolled Subjects

This data set will contain available data from all enrolled subjects, including those who did not receive any study treatment. This data set will be used for analysis of subject disposition.

11.2.2 Efficacy

The efficacy data set will include data from all enrolled subjects who receive any amount of study treatment.

11.2.3 Safety

The safety data set will be the same as the efficacy data set, which includes data from all enrolled subjects who receive any amount of study treatment. In the safety analysis, no data exclusion is allowed because of protocol deviations.

11.2.4 Pharmacokinetics

The PK data set will include all available plasma concentrations for decitabine, E7727, and E7727-epimer for subjects who have received study treatment. PK parameters will be derived for all PK-evaluable subjects, provided sufficient data points are available.

11.2.5 Pharmacodynamics and Biomarker Analyses

Subjects will be included in the PD and biomarker analyses if their DNA global methylation (LINE-1) data or biomarker data are successfully collected and tested.

11.3 Schedule of Analyses

Analyses of safety, efficacy, PD, and PK data will be regularly performed for review by the DSRC for the purpose of guiding decisions such as dose escalation, de-escalation, and change in cohort size, determination of subsequent dose level during the Dose Escalation Stage. Final and complete analyses of all data, however, will be performed at the end of the Dose Confirmation Stage after all subjects have completed at least two courses of therapy (as planned). Additional survival analysis based on long-term follow-up may be conducted as needed.

In the Dose Confirmation Stage, the DSRC will review data from the first 6-12 subjects with complete PK and PD data from the first 2 courses to confirm the doses used for ASTX727 components. If a dose change is required, another assessment of PK and PD data will be done after 6-12 subjects have received the new doses.

In the FDC Stage, data from subjects who have complete PK and PD data from Courses 1 and 2 of the FDC Stage will be reviewed to confirm that data with the FDC tablet are similar to data with IV decitabine.

No formal interim analyses are planned for this study.

11.4 Analysis of Subject Disposition

The number and percentage (n, %) of subjects enrolled, treated, lost to follow up, and withdrawn (with reason) will be summarized by study stage. The All Enrolled Subject Data Set will be used for disposition analysis. The number screened and reasons for screen fails will be noted if the information is available.

The number of subjects transitioned from E7727 + decitabine capsules to the ASTX727 FDC tablet will be summarized by subjects' original study stage and treatment cohorts.

11.5 Analysis of Demographic and Baseline Data

Subject demographic and baseline characteristics will be summarized using mean, standard deviation, median, minimum, and maximum for continuous variables, and by counts and percentages for categorical variables based on all treated subjects (safety and efficacy dataset). Summaries will be provided separately by stage of study and, if deemed necessary, by dose cohort or treatment sequence.

11.6 Efficacy Analyses

Efficacy analyses will be conducted based on all treated subjects (efficacy dataset) by stage of the study, and if deemed necessary, by dose cohort (Dose Escalation Stage).

Response rates and rates of hematologic improvement will be calculated as defined by the IWG 2006 MDS Response Criteria. The 95% CIs will be estimated for the response rate calculated. Duration of response (in number of days) will be calculated from the first time the response is observed to time of relapse or last time point in the study. Rate of transfusion independence will be calculated based on the number of transfusion-dependent subjects who had no transfusion for at least 56 days during treatment.

Overall survival will be defined as the number of days from the day the subject received the first dose of IV decitabine, oral decitabine + E7727, or the FDC tablet, to the date of death (regardless of cause). Time to AML will be the number of days from the day the subject received the first dose of IV decitabine, oral decitabine + E7727, or the FDC tablet, to the date of death or the date of MDS progression to AML as defined by ≥20% blasts in bone marrow or peripheral blood using the WHO classification. Both of these time-to-event endpoints will be evaluated using the Kaplan-Meier method. Survival time and time to AML will be censored on the last date of contact if a subject is lost to follow up prior to reaching a time-to-event endpoint.

11.7 Safety Analyses

Safety analyses include the analyses of AEs, DLTs, concomitant medications, laboratory values, vital signs and ECG assessments. Safety analyses will be conducted on all treated subjects (safety dataset), by stage of study and dose cohort as appropriate.

AE terms reported by study subjects or observed by investigators will be mapped to the appropriate system organ class (SOC) and preferred term (PT) according to the MedDRA version 16.0. Severity of AE will be graded using NCI CTCAE version 4.0. All adverse events will be listed. Treatment-emergent adverse events (TEAEs) will be summarized using counts and percentages by MedDRA SOC and PT and by CTC AE grades. TEAEs are defined as events that occurred or worsened after the first dose of study treatment. Summaries of all TEAEs, all related TEAEs, all serious TEAEs and all serious related TEAEs will be provided.

DLTs are defined in Section 4.5. Instances of DLTs will be identified in each dose cohort and listed separately to assist in determining the desired dose level for the combination of oral decitabine + E7727 in the Dose Escalation Stage. DLTs will be summarized by severity and seriousness (Y/N), as well as relationship to the study treatment.

Concomitant medications will be coded according to the WHO DRUG Dictionary (December 2012 version) and summarized by Therapeutic subgroup (ATC level 2) and generic name. Concomitant medications are the medications taken with a start date on or after the start of the administration of the study treatment.

Laboratory values will be listed. Laboratory values will also be graded, if possible and deemed necessary, by CTCAE in conjunction with the Harrison (18th edition) lab book normals. Shift tables will display (1) shift from baseline to worst laboratory value grade during the study, and (2) shift from baseline to last lab value grade at the end of the study.

Vital Signs will be summarized by visit using proportion of subjects with each vital sign being too high or too low according to the conventionally accepted vital sign normal ranges.

For analysis of ECGs, QTc will be coded using CTCAE 4.0, and shift tables will be used to show the shift from baseline grade to worst grade and from baseline to the last visit QTc grade.

11.8 Pharmacokinetic/Pharmacodynamic/Biomarker Analyses

11.8.1 Pharmacokinetic Analyses

The PK data set will be used for analysis of all PK parameters. PK parameters of decitabine, E7727, and E7727-epimer will be derived for each subject using a non-compartmental approach.

PK parameters will be summarized descriptively using mean, standard deviation, median and range by dose cohort and course/days, and by stage of the study if deemed necessary. In particular, PK values obtained after oral decitabine + E7727 or the FDC tablet will be compared descriptively with those after IV decitabine on intra-subject basis and also by dose/cohort average basis.

In addition, the decitabine AUC values obtained from the 2 x 2 crossover design part of the study (Dose Confirmation and FDC Stages) will be analyzed for equivalence of means using the confidence interval (CI) method. The AUC values from the two treatments are considered comparable for the purpose of this phase 1-2 study, if the two-sided 80% CI of the mean AUC ratio lies entirely within the range of 0.75 – 1.33 in the Dose Confirmation Stage or 0.65-1.539 in the FDC Stage.

PK dose proportionality will be tested using linear regression between dose and dose-adjusted parameter estimates; correlation of PK to PD will be assessed.

11.8.2 Pharmacodynamic/Biomarker Analyses

Subjects will be included in the PD and biomarker analyses if their DNA global methylation (LINE-1) data or biomarker data are successfully collected and tested. PD and biomarkers will be summarized descriptively (using mean, standard deviation, median and range for continuous variables and counts and percentages for categorical variables) by dose cohort and course/days, and by stage of the study if deemed necessary.

In addition, the mean maximum %LINE-1 demethylation from baseline obtained from the 2 x 2 crossover design part of the study will be analyzed for non-inferiority of means (oral decitabine + E7727 compared with IV decitabine in the Dose Confirmation Stage, and the FDC tablet compared with IV decitabine in the FDC Stage) using the confidence interval (CI) method. Oral decitabine + E7727 is considered non-inferior to IV decitabine with respect to LINE-1 demethylation, for the purpose of this phase 1-2 study, if the upper bound of the two-sided 80% CI of the difference in mean maximum %LINE-1 demethylation between oral decitabine + E7727 and IV decitabine is below 0.05 in the Dose Confirmation Stage. In the FDC Stage, the upper bound of the two-sided 80% CI for the difference of mean maximum %LINE-1 demethylation between the FDC tablet and IV decitabine must be <0.075 to achieve non-inferiority. The details of this analysis will be defined in the statistical analysis plan.

Additional biomarker analysis will include assessment of baseline CDA activity and changes in circulating [redacted] levels post-treatment.

11.9 Interim Analysis

No formal interim analysis is planned for this study. However, safety data will be routinely reviewed, and a thorough review of safety data will be conducted after every cohort of at least 3 subjects during the Dose Escalation Stage, at the end the Dose Escalation Stage, and at least quarterly during the Dose Confirmation Stage. In addition, during the Dose Confirmation Stage and FDC Stage, data assessments will be conducted by the DSRC as described above in Section 11.3.

11.10 Procedures for Handling Missing, Unused, and Spurious Data

No imputation of values for missing data will be performed, unless otherwise specified. Data from subjects lost to follow up will be included in statistical analyses up to the time of last evaluation. Data from all enrolled subjects will be included in the data listings, and summary tables (with the exception of the subject disposition table) will be based on data from all treated subjects. Actions on spurious data, if any, will be described fully in the clinical study report.

12.0 STUDY DURATION AND TERMINATION

The study is expected to start in Q2 2014. The Dose Escalation Stage is expected to take 12 months, and the Dose Confirmation Stage is expected to take approximately 12 months. The FDC Stage is expected to take approximately 12 months.

13.0 STUDY COMPLIANCE AND ETHICAL CONSIDERATIONS

13.1 Compliance Statement

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

13.2 Informed Consent

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

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

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

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

14.0 ADMINISTRATIVE PROCEDURES

14.1 Sponsor's Responsibilities

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

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

14.1.1 Study Supplies

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

- Oral decitabine + E7727 as described in Section 7.0.
- Decitabine IV to Canadian study centers (see Section 14.2.2).
- FDC tablet as described in Section 7.0.
- Case Report Forms or data collection tools.

14.1.2 Investigator Training

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

14.1.3 Ongoing Communication of Safety Information during the Study

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

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

14.1.4 Study Monitoring

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

- Assure compliance with the study protocol and appropriate regulations.
- Verify that (1) the informed consent process was conducted before initiation of any study-specific procedures (i.e., performed solely for the purpose of determining eligibility for the study) and before provision of study treatment, and (2) this process is adequately documented.
- Verify that the protocol, protocol amendments, and safety information are submitted to the IRB/IECs and approved by the IRB/IECs in a timely manner.
- Review the eCRFs and source documents to ensure that reported study data are accurate, complete, and verifiable from source documents.
- Verify that study treatments are stored properly and under the proper conditions, that they are in sufficient supply, and that receipt, use, and return of oral decitabine + E7727 at the study centers are controlled and documented adequately.
- Verify that the investigator and study center personnel remain adequately qualified throughout the study.
- Verify that the research facilities, including laboratories and equipment, are maintained adequately to safely and properly conduct the study.

14.1.5 Study Auditing and Inspecting

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

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

14.2 Investigator's 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 Decitabine, E7727, and FDC Tablet Accountability

Initial supply of E7727 and decitabine capsules (ie, not decitabine IV) will be provided to US sites, as decitabine IV is commercially available in the US. However, E7727 and decitabine (capsules and IV) will be provided by Astex to Canadian sites, as decitabine IV is not approved in Canada. Thereafter, the study pharmacist is responsible for ordering resupplies.

The FDC tablet will be supplied by Astex to all study centers.

Keep E7727 and decitabine in a locked, limited-access room. The study treatment must not be used outside the context of the protocol. Under no circumstances should the investigator or other study center personnel supply E7727 or decitabine 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 E7727 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 E7727 and/or decitabine and other study material is destroyed or returned to the sponsor on completion of the study. If E7727 and/or decitabine is destroyed at the study center, there should be documentation of destruction at the study center. The sponsor and/or their representatives will verify final drug accountability. Drug 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, (e.g., 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 components samples which are collected as part of routine medical care or as part of protocol procedures may be stored and analyzed for PK or PD 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)'s Reflection Paper on Pharmacogenomic Samples, Testing and Data Handling (EMEA 2007). Astex Pharmaceuticals, Inc. will not store study samples in a biobank.

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 DSRC safety decisions for immediate implementation for safety reasons (Section 4.4).

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

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

15.0 POLICY FOR PUBLICATION AND PRESENTATION OF DATA

The sponsor encourages the scientific publication of data from clinical research studies. However, investigators may not present or publish partial or complete study results individually without

review by the sponsor. The principal investigators and the sponsor may propose appropriate scientific manuscripts or abstracts from the study data. The sponsor must review and comment on all proposed publications before submission for publication. The detailed procedures for the review of publications are set out in the clinical trial agreement entered into with the sponsor in connection with this study. These procedures are in place to ensure coordination of study data publication and adequate review of data for publication against the validated study database for accuracy. Names of all investigators and sponsor representatives responsible for designing the study and analyzing the results will be included in the publication(s).

Qualification of authorship will follow the requirements of the International Committee of Medical Journal Editors (www.icmje.org). In most cases, the principal investigators at the centers with the highest participation and accruals of eligible subjects and data in the study shall be listed as lead authors on manuscripts and reports of study results. The sponsor's medical monitor, study director and/or lead statistician may also be included in the list of authors. This custom can be adjusted upon mutual agreement of the authors and Astex Pharmaceuticals. In addition, other than clinical pharmacology studies in healthy volunteers or Phase 1 studies, all clinical studies must be registered with ClinicalTrials.gov.

16.0 REFERENCES

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Dacogen. Dacogen (decitabine for injection) Prescribing Information. 2014.

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17.0 APPENDICES

APPENDIX 1: COMMON TERMINOLOGY FOR ADVERSE EVENTS V4.0 (CTCAE V4.0)

For links to the NCI-CTCAE version 4, refer to

HTTP://CTEP.CANCER.GOV/PROTOCOLDEVELOPMENT/CODES_VALUES.HTM#CTC

APPENDIX 2: SCHEDULE OF PHARMACOKINETIC ASSESSMENTS

The schedule for PK assessments is shown in the tables on the following pages.

	Pharmacokinetics Sampling Schedule for the Dose Escalation Stage											
	Course 1						**Course 2**					
	Day -3 (±2)	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day -3 (±2)**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**
Study Treatment	oral decitabine	IV decitabine	Oral decitabine + E7727				E7727	Oral decitabine + E7727				
Pre-dose (Time 0)	x	x	x	x[a]	x	x	x					
Time point after dosing or start of infusion (hour):												
0.25	x	x	x			x	x					
0.5	x	x	x			x	x					
1	x	x[b]	x			x	x					
1.083 (1 hour 5 min)		x[c]										
1.5	x	x	x			x	x					
2	x	x	x			x	x					
3	x	x	x			x	x					
4	x	x	x			x	x					
6	x	x	x			x	x					
8			x			x	x					
24[a]			x[a]				x[a]					

[a] The pre-dose time point is same as 24-hour time point on previous day; the 24-hour time point is the same as the pre-dose time point on the following day.
[b] The 1-hour sample should be taken immediately prior to the end of the decitabine infusion.
[c] The 1-hour, 5-min sample should be taken 5 minutes after completion of the decitabine infusion.
NOTE: PK evaluation includes decitabine, E7727, E7727-epimer, [redacted].
NOTE: Volume per blood draw = 3 mL. Total blood draw for Course 1 + Course 2 = 156 mL. No more than 33 mL of blood will be drawn in any 24-hour period. Additional information regarding sample collection, processing, etc., will be provided in the laboratory manual.
NOTE: PK sampling should take place within ±10% of the scheduled time point, not to exceed 1 hour at the 24-hour time point.

		Pharmacokinetics Sampling Schedule for Dose Confirmation Stage									
Study Treatment		**IV decitabine in Course 1**					**Oral Decitabine + E7727 in Course 2**				
		Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**
If randomized to sequence of Course 1: IV decitabine Course 2: oral decitabine + E7727	**Pre-dose (Time 0)**	x					x	x[a]	x	x	x
	Time point after oral dose or start of infusion (hour):										
	0.25	x					x	x			x
	0.5	x					x	x	x	x	x
	1	x[b]					x	x	x	x	x
	1.083 (1 hour 5 min)	x[c]									
	1.5	x					x	x			x
	2	x					x	x	x		x
	3	x					x	x		x	x
	4	x					x	x			x
	6	x					x	x			x
	8						x	x			x
	24[a]						x[a]	x[a]			

[a] The pre-dose time point is same as 24-hour time point on previous day; the 24-hour time point is the same as the pre-dose time point on the following day.
[b] The 1-hour sample should be taken immediately prior to the end of the decitabine infusion.
[c] The 1-hour, 5-min sample should be taken 5 minutes after completion of the decitabine infusion.
NOTE: PK evaluation includes decitabine and E7727 (required) and E7727-epimer and cytidine (if needed) - in Dose-Confirmation Stage when receiving the oral combination.
NOTE: Volume per blood draw = 3 mL. The total blood volume planned for Course 1 + Course 2 = ~150 mL. The blood draw schedule may be modified during Dose Confirmation to eliminate certain days and/or time points. The total number of blood draws in Dose Confirmation will not increase from the above schedule but may decrease after assessment of PK data from the first 12-24 subjects. Additional information regarding sample collection, processing, etc., will be provided in the laboratory manual.
NOTE: PK sampling should take place within ±10% of the scheduled time point, not to exceed 1 hour at the 24-hour time point.

		Pharmacokinetics Sampling Schedule for Dose Confirmation Stage									
Study Treatment		**Oral Decitabine + E7727 in Course 1**					**IV decitabine in Course 2**				
		Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**
If randomized to sequence of Course 1: Oral decitabine + E7727 Course 2: IV decitabine	**Pre-dose (Time 0)**	x	x[a]	x	x	x	x				
	Time point after oral dose or start of infusion (hour):										
	0.25	x	x			x	x				
	0.5	x	x	x	x	x	x				
	1	x	x	x	x	x	x[b]				
	1.083 (1 hour 5 min)						x[c]				
	1.5	x	x			x	x				
	2	x	x	x		x	x				
	3	x	x		x	x	x				
	4	x	x			x	x				
	6	x	x			x	x				
	8	x	x			x					
	24[a]	x[a]	x[a]								

[a] The pre-dose time point is same as 24-hour time point on previous day; the 24-hour time point is the same as the pre-dose time point on the following day.
[b] The 1-hour sample should be taken immediately prior to the end of the decitabine infusion.
[c] The 1-hour, 5-min sample should be taken 5 minutes after completion of the decitabine infusion.
NOTE: PK evaluation includes decitabine and E7727 (required) and E7727-epimer and cytidine (if needed) - in Dose-Confirmation Stage when receiving the oral combination.
NOTE: Volume per blood draw = 3 mL. Total blood volume planned for Course 1 + Course 2 = ~150 mL. The blood draw schedule may be modified during Dose Confirmation to eliminate certain days and/or time points. The total number of blood draws in Dose Confirmation will not increase from the above schedule but may decrease after assessment of PK data from the first 12-24 subjects. Additional information regarding sample collection, processing, etc., will be provided in the laboratory manual.
NOTE: PK sampling should take place within ±10% of the scheduled time point, not to exceed 1 hour at the 24-hour time point.

		Pharmacokinetics Sampling Schedule for FDC Stage									
Study Treatment		**IV decitabine in Course 1**					**FDC in Course 2**				
		Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**
If randomized to sequence of Course 1: IV decitabine Course 2: FDC tablet	**Pre-dose (Time 0; within 1 hour pre-dose)**	x					x	x[a]	x	x	x
	Time point after oral dose or start of infusion (hour) and window:										
	0.25 (15 ± 1.5 min)	x					x				x
	0.5 (30 ± 3 min)	x					x				x
	1 (within 5 min before completion of IV infusion - see Tasks below)	x[b]					x				x
	1.083 (5 min + 0.5 min)	x[c]									
	1.5 (30 min ± 3 min)	x					x				x
	2 (± 12 min)	x					x				x
	3 (± 18 min)	x					x				x
	4 (± 24 min)	x					x				x
	6 (± 36 min)	x					x				x
	8 (± 48 min)						x				x
	24[a]						x[a]				

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

[b] Obtain the 1-hour sample at the end of infusion: the sample should be collected during the final 5 minutes of infusion while drug is being administered. Do not obtain after the infusion has stopped. (2) Conclude the infusion as soon as practically possible after the sample has been obtained; disconnect the drug infusion bag, bolus flush drug out of the line with IV fluid, and start a drug-free drip. (3) Start the clock for post infusion immediately after the flush.

[c] The 1-hour, 5-min sample should be taken 5 minutes after completion of the decitabine infusion.

NOTE: Volume per blood draw = 3 mL. The total blood volume planned for Course 1 + Course 2 = ~105 mL. The blood draw schedule may be modified during this stage to eliminate certain days and/or time points. The total number of blood draws will not increase from the above schedule but may decrease after assessment of PK data from the first 12-18 subjects. Additional information regarding sample collection, processing, etc., will be provided in the laboratory manual.

NOTE: PK sampling should take place within ±10% of the scheduled time point, not to exceed 1 hour at the 24-hour time point.

Study Treatment		Pharmacokinetics Sampling Schedule for FDC Stage									
		FDC in Course 1					IV decitabine in Course 2				
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 1	Day 2	Day 3	Day 4	Day 5
If randomized to sequence of Course 1: FDC tablet Course 2: IV decitabine	Pre-dose (Time 0; within 1 hour pre-dose)	x	x[a]	x	x	x	x				
	Time point after oral dose or start of infusion (hour) and window:										
	0.25 (15 ± 1.5 min)	x				x	x				
	0.5 (30 ± 3 min)	x				x	x				
	1 (within 5 min before completion of IV infusion - see Tasks below)	x				x	x[b]				
	1.083 (5 min + 0.5 min)						x[c]				
	1.5 (30 min ± 3 min)	x				x	x				
	2 (± 12 min)	x				x	x				
	3 (± 18 min)	x				x	x				
	4 (± 24 min)	x				x	x				
	6 (± 36 min)	x				x	x				
	8 (± 48 min)	x				x					
	24[a]	x[a]									

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

[b] Obtain the 1-hour sample at the end of infusion: the sample should be collected during the final 5 minutes of infusion while drug is being administered. Do not obtain after the infusion has stopped. (2) Conclude the infusion as soon as practically possible after the sample has been obtained; disconnect the drug infusion bag, bolus flush drug out of the line with IV fluid, and start a drug-free drip. (3) Start the clock for post infusion immediately after the flush.

[c] The 1-hour, 5-min sample should be taken 5 minutes after completion of the decitabine infusion.

NOTE: Volume per blood draw = 3 mL. The total blood volume planned for Course 1 + Course 2 = ~105 mL. The blood draw schedule may be modified during this stage to eliminate certain days and/or time points. The total number of blood draws will not increase from the above schedule but may decrease after assessment of PK data from the first 12-18 subjects. Additional information regarding sample collection, processing, etc., will be provided in the laboratory manual.

NOTE: PK sampling should take place within ±10% of the scheduled time point, not to exceed 1 hour at the 24-hour time point.

APPENDIX 3: ECOG AND KARNOFSKY PERFORMANCE STATUS

Score	ECOG Description	Score	Karnofsky Description
0	Fully active, able to carry on all predisease performance without restriction	100	Normal: no complaints, no evidence of disease
		90	Able to carry on normal activity; minor symptoms
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; some symptoms
		70	Cares for self; unable to carry on normal activities
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 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: hospitalized but death not imminent
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair	20	Very sick: active supportive care needed
		10	Moribund: fatal processes are progressing rapidly
5	Dead	0	Dead

Sources:

ECOG Performance Status — http://www.ecog.org/general/perf_stat.html (accessed August 30, 2007).

Karnofsky Performance Status — http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/neurology/braintumor/table3.htm (accessed February 11, 2008).

APPENDIX 4: SUMMARY OF CHANGES, AMENDMENT 1

Rationale for Amendment 1:

The following main changes have been made in Amendment 1 to facilitate arrival at an optimal dose earlier during the course of the trial, to reduce subject exposure to subtherapeutic doses, and to reduce the burden of assessments:

- The study design has been modified from a 6+6 design to a 3+3 design to allow dose escalation if the PK data are consistent across the first 3 subjects in a given cohort and no DLTs are observed. At least another 3 subjects are to be enrolled in that cohort if the PK data are variable across the first 3 subjects or if 1 DLT occurs. The Data and Safety Review Committee will continue to conduct routine review of safety and PK data.
- The requirement for hematology assessments has been eliminated on Days 2-5 in Course 1 and Course 2, as weekly hematology assessments are sufficient with decitabine therapy. Hematology will continue to be assessed on Days 1, 8, 15, and 22 of the first 2 courses.

Summary of Changes:

Typographical errors have been corrected and minor changes to the text that have been made for clarity are not summarized below.

1) Header: IND number removed, as some study centers are ex-US.
2) PROTOCOL TITLE PAGE: EudraCT Number added.
3) PROTOCOL SYNOPSIS:
   a) Study Centers Planned/Country: Canada added.
   b) Study Design and Investigational Plan: Dose Escalation Stage: changed from 6+6 to 3+3.
   c) Sample Size and Statistical Analyses: Clarification made that when the AUC range for a 3-subject cohort is between 0.90-1.10 of IV decitabine, and no more than 1 DLT has occurred, additional evaluable subjects may be added (for up to 12-18 in that cohort).
   d) Study Duration and Termination: duration of the Dose Escalation Stage revised to 12 months.
4) Section 4.1.1: changed to 3+3 design; modified to reflect the change from 6+6 to 3+3. Additional subjects may be added to reach a total of up to 12-18 subjects in a cohort for robust assessment of AUC range and safety before moving to the Dose Confirmation Stage.
5) Figure 2: revised in accordance with changes to study design.
6) Section 4.2: changed to 3+3 design.
7) Section 4.4: change made to allow DSRC to increase a cohort size to a total of up to 12-18 additional subjects.

8) Section 5.1: changed to 3+3 design.

9) Section 5.2: Inclusion criterion 4a clarified to indicate omission of AST assessment will not be considered a protocol deviation.

10) Table 4: Schedule of Events:

    a) Physical exam: required on Days 2-5 only if subject is visiting the clinic for study purposes.

    b) Vital signs: required on Days 2-5 only if subject is visiting the clinic for study procedures.

    c) Concomitant medications and transfusion requirements: may be assessed on Days 2-5 if subject is visiting the clinic for study procedures.

    d) Hematology: assessments on Days 2-5 in Course 1 and Course 2 removed.

11) Section 9.4.3.3: Clarification made that the indicated assessments are to be done on days the subject comes to the clinic for IV decitabine or PK assessments. Collection of hematology samples has been removed.

12) Section 9.4.3.5: Clarification made that symptom-directed physical exam and vital signs may be completed if subject is visiting the clinic for study procedures.

13) Section 9.4.4: Clarification made that symptom-directed physical exam and vital signs (Days 2-5) may be completed if subject is visiting the clinic for study procedures. Collection of hematology samples on Days 2-5 has been removed.

14) Section 11.1.1: Changed from 6+6 to 3+3 design.

15) Section 11.9: Review of safety data changed from after every cohort of 6 to after every cohort of at least 3 subjects (during Dose Escalation).

16) Section 12.0: Duration of Dose Escalation Stage revised to 12 months.

APPENDIX 5: SUMMARY OF CHANGES, AMENDMENT 2

Rationale for Amendment 2:

The following main changes have been made in Amendment 2:

- Eliminate the Dose Confirmation – Open Label Expansion portion of the study. This portion may not add significant value, as PK, PD, efficacy, and safety will be adequately assessed in the randomized part of the Dose Confirmation Stage.
- Obtain additional PK assessments on Days 2, 3, and 4 during the oral course of the Dose Confirmation Stage to enable estimation of PK over 5 dosing days. This is prompted by the expected variation in decitabine PK levels after Day 1 of oral dosing compared with Days 2-5, based on data from the Dose Escalation Stage.
- Clarify that PK and PD data reviews by the DSRC will take place during the Dose Confirmation Stage to ensure that the doses of the 2 components of ASTX727 result in the desired PK and PD comparability with IV decitabine.
- Incorporate items from Administrative Letters 2, 3, and 4:
    - Administrative Letter #2: Clarification that initial supplies of E7727 and decitabine (capsules and IV) will be provided to Canadian study centers, as decitabine IV is not approved in Canada. Clarification that subjects should take the IMPs simultaneously and at the same time of day (± 1 hour) on each dosing day.
    - Administrative Letter #3: Clarification to allow intra-patient dose escalation to a higher dose established as safe in a subsequent cohort. Instructions added for situations in which a dose is missed.
    - Administrative Letter #4: Clarification that study centers may follow a schedule according to local standard practice after Course 7 for bone marrow aspirate or biopsy to verify continuous response.

Summary of Changes:

Typographical errors have been corrected and minor changes to the text that have been made for clarity are not summarized below.

1) **PROTOCOL TITLE PAGE** and **SPONSOR AND INVESTIGATOR SIGNATURE PAGE**: Address for Astex Pharmaceuticals, Inc. updated. Medical Monitor information updated.

2) PROTOCOL SYNOPSIS:

- Dose Confirmation Stage – Open-Label Expansion eliminated.
- Dose Confirmation Stage Primary Objectives: Clarification that mean oral decitabine AUC will be estimated from 5 days of dosing.

- Inclusion Criterion #2: a, b, and c removed.
- Dose Confirmation Stage Primary Endpoint – Clarification that mean decitabine AUC will be an estimate over 5 dosing days.
- Sample size for Dose Escalation Stage: Revised from 1 DLT in 12 subjects to 1 DLT in 6 subjects.
- Sample Size for Dose Confirmation Stage – Changed to at least 42 subjects at the final recommended dose combination.
- Interim Analysis: Text added to indicate that ongoing data review will be performed by the Data and Safety Review Committee (DSRC).

3) **Section 3.4, Dose Confirmation Stage – Primary Objectives:** Clarification that the mean oral decitabine AUC will be estimated from 5 days of dosing.
4) **Section 4.1.1, Dose Escalation Stage, Dosing for Cohort ≥2:** Modified to allow intra-patient dose escalation for subjects who are still on treatment at lower dose levels in the Dose Escalation Stage once higher levels are deemed to be safe by DSRC review.
5) **Figure 2, Dose Escalation Stage Algorithm:** Updated to align with amendment.
6) **Figure 3, Dose Confirmation Stage Schema:** Updated to align with amendment (Open-label expansion removed).
7) **Section 4.2, Discussion of Study Design:** Clarification that estimated PK over 5 days of dosing will be used to compare oral combination and IV decitabine. Open-label expansion text removed.
8) **Section 4.3.4, Dose Confirmation Stage – Primary Endpoints:** Clarification that mean decitabine AUC will be an estimate over 5 dosing days.
9) **Section 4.4, Data Safety and Review Committee (DSRC):** New text added (last paragraph) to indicate the DSRC will review safety, PK, and PD data during the Dose Confirmation Stage and determine a final dose combination.
10) **Section 5.1, Number of Subjects and Centers:** Text modified to at least 42 subjects at the final recommended dose combination.
11) **Section 5.2, Inclusion Criteria, #2:** a, b, and c removed.
12) **Section 5.2, Inclusion Criteria, #4a:** "Omission of AST assessment at screening or during the study is not considered a protocol deviation" removed.
13) **Section 7.1.2, Storage:** New statement added as 1st paragraph for clarification: "The IV decitabine drug product is sourced from commercial supplies and should be stored according to institutional policy and the manufacturer's label."
14) **Section 7.1.5, Missed Doses:** New section added to describe the procedure in the event a dose is missed.

15) **Section 7.2, Active Comparator or Placebo:** Statement added to indicate that decitabine IV will be provided by Astex as an IMP in Canada (as decitabine is not currently approved in Canada).

16) **Section 9.1, Efficacy Assessments:** Clarified to indicate that after Course 7, bone marrow aspirates may be performed according to a schedule that is standard practice at the study center.

17) **Section 9.2.1.3, Dose Confirmation Stage:** PK assessments have been added to Day 2, Day 3, and Day 4, with additional explanatory text.

18) **Table 3, Dosing Schedule by Stage and Course:** Dose Confirmation Stage – Open Label Expansion information has been removed.

19) **Table 4, Schedule of Events:** Footnote 'w': wording modified to align with Administrative Letter #4.

20) **Table 6, Day 1 Assessments:** Dose Confirmation Stage – Open Label Expansion column removed.

21) **Section 9.4.5.1, Course ≥3, Days 1-5 – Dose Escalation Stage and Dose Confirmation Stage:** Bone marrow aspirate or biopsy: Revised to indicate that after Course 7, study centers may assess according to a schedule that is standard of care at the center (this aligns with Administrative Letter #4).

22) **Section 11.1.2, Dose Confirmation Stage:** revised from 84 to at least 42 subjects.

23) **Section 11.3, Schedule of Analysis:** 2nd paragraph added to indicate that the DSRC will review data from the first 6-12 subjects with complete PK and PD data from Courses 1 and 2 to confirm the dose combination.

24) **Section 11.8.1, Pharmacokinetic Analyses:** Statement added to 3rd paragraph to clarify that AUC will be estimated over 5 days of dosing.

25) **Section 11.9, Interim Analysis:** Statement added to emphasize DSRC review during the Dose Confirmation Stage.

26) **Section 14.1.1, Study Supplies:** Bullet added to indicate that IV decitabine will be provided by Astex to Canadian sites.

27) **Section 14.2.2, Decitabine and E7727 Accountability:** Text added to clarify provision of IMPs.

28) **Section 14.2.5, Tissue and Blood Sample Collection/Storage:** 2nd paragraph, last sentence added to clarify that Astex does not intend to store samples at a biobank.

29) **Appendix 2, Schedule of Pharmacokinetic Assessments:** sampling schedule for Dose Confirmation Stage has been modified to include sampling on Days 2, 3, and 4. Total blood volume revised from 99 mL to ~150 mL for Courses 1 and 2.

APPENDIX 6: SUMMARY OF CHANGES, AMENDMENT 3

Rationale for Amendment 3:

The main changes described below have been made in Amendment 3 to add a third stage to the study to confirm the FDC tablet formulation yields PK and PD data similar to data for IV decitabine and to gather additional efficacy and safety data with the FDC in 18-24 subjects.

In addition, the clarification made in Administrative Letter #5 has been incorporated: Inclusion Criterion #2 applies to subjects enrolled in all stages of the study, including the FDC Stage.

The main changes in this amendment are listed below. Minor changes to the text that have been made for clarity are not listed.

1) **PROTOCOL SYNOPSIS:**
   a. Investigational Medicinal Product: A description of the FDC tablet has been added.
   b. Dose Confirmation Stage – Exploratory Objective and Endpoint changed to: [redacted]
   c. FDC Stage: Study Objectives added.
   d. Study Design and Investigational Plan: a description of the FDC Stage has been added.
   e. Study Treatment: Statement added that the FDC tablet is to be administered at the same time of day, with water, with the subject in a fasted state.
   f. Study Endpoints for the FDC Stage have been added.
   g. Sample Size and Statistical Analysis: Sample size justification for the FDC Stage has been added.
   h. Study Duration and Termination: Estimated duration (12 months) for the FDC Stage has been added.
2) **Abbreviations and Definitions:** FDC has been added and defined.
3) **Section 1.3.3:** Opening statement added to indicate that preliminary data from the study were used to inform the strength of the FDC tablet.
4) **Section 2.2:** Statement added at end of section to indicate that preliminary data from the study were used to inform the strength of the FDC tablet.
5) **Sections 3.7, 3.8, 3.9:** Primary, secondary, and exploratory objectives added, respectively, for the FDC Stage.
6) **Section 4.1:** FDC Stage added to the opening sentence.
7) **Figure 2:** CMML has been added to the 'Dose Escalation Algorithm' box.
8) **Figure 3:** CMML has been added to the description of subjects.
9) **Section 4.1.3:** A description of the FDC study design and investigational plan has been added.
10) **Figure 4:** New figure added showing the study schema for the FDC Stage.

11) **Section 4.2:** A brief description of the goal of the FDC Stage has been added as the 4th paragraph.

12) **Section 4.3.6:** Dose Confirmation Stage Exploratory Endpoint changed to: [redacted]

13) **Sections 4.3.7, 4.3.8, 4.3.9:** Study endpoints for the FDC Stage have been added.

14) **Section 4.4:** Bullet statement added regarding the frequency with which the DSRC will meet to review data from the FDC Stage.

15) **Section 6.2:** Explanation of randomization and the treatment groups for the FDC Stage, and statement added that subjects with CMML will be randomized in the IPSS-2/high-risk stratum (as IPSS risk level is not applicable to subjects with CMML).

16) **Section 7.1.1:** A description of the FDC tablet has been added.

17) **Section 7.1.2:** Storage instructions for the FDC tablet have been added.

18) **Section 7.3:** Instructions for dose reduction have been added.

19) **Section 9.2.1.4:** PK sampling schedule for the FDC Stage has been added.

20) **Section 9.2.2.3:** LINE-1 DNA methylation assessment schedule for the FDC Stage added.

21) **Table 3:** Dosing schedule for the FDC Stage has been added.

22) **Table 4:** Title modified and PK sampling schedule for the FDC Stage added. Footnotes edited for clarification.

23) **Section 9.4.2:** Bullet added to indicate that a portion of Screening bone marrow aspirates will be used for assessing [redacted].

24) **Table 6:** Day 1 assessments for the FDC Stage have been added.

25) **Section 9.4.3.2:** Study treatment administration instructions for the FDC Stage have been added.

26) **Section 9.4.3.3:** Study treatment administration instructions for the FDC Stage have been added.

27) **Section 9.4.4:** Study treatment administration instructions for the FDC Stage have been added.

28) **Section 9.4.5.1:** Statement added to indicate that a portion of bone marrow aspirates will be used for assessing [redacted].

29) **Section 11.1.3:** Sample size justification for the FDC Stage has been added.

30) **Section 11.3:** Paragraph added to explain timing of data review in the FDC Stage.

31) **Section 11.6:** 'FDC tablet' added where indicated.

32) **Section 11.8.1:** 'FDC tablet' added where indicated, and range of the two-sided 80% CI of the mean AUC ratio in FDC Stage added.

33) **Section 11.8.2:** Statement added regarding upper bound of the two-sided 80% CI for the difference of mean maximum %LINE-1 demethylation between the FDC tablet and IV decitabine.

34) **Section 12.0:** Estimated duration (12 months) for the FDC Stage has been added.

35) **Section 14.1.1:** Bullet statement added to indicate information for FDC tablet is provided in **Section 7.0**.

36) **Section 14.2.2:** Statement added after first paragraph to indicate FDC tablet will be supplied by Astex.

37) **Appendix 2:** PK sampling schedules for the FDC Stage have been added.

APPENDIX 7: SUMMARY OF CHANGES, AMENDMENT 4

Rationale for Amendment 4:

Subjects ongoing in either the Dose Escalation Stage or Dose Confirmation Stage are allowed to transition from E7727 and oral decitabine capsules to the more convenient FDC tablet, which has the optimal dose combination of E7727 and decitabine that emulates the PK and PD of decitabine IV 20 mg/m^2. The specified date of transition is based on the supply expiry date of the capsules.

Clarification made in Administrative Letter #6 (dated 03 October 2016) has been incorporated: the 8-hour time point for PK measurement on Day 1 of the IV decitabine course that erroneously appeared in the tables for "Pharmacokinetic Sampling Schedule for FDC Stage" in Appendix 2 (Protocol Amendment 3) has been removed.

The main changes in this amendment are listed below. (Typographical errors have been corrected.)

PROTOCOL SYNOPSIS:

Study Design and Investigational Plan: Information regarding transition from E7727 + decitabine capsules to the ASTX727 FDC tablet added for subjects ongoing in the Dose Escalation and Dose Confirmation Stages.

Study Assessments and Procedures: Last paragraph: Language added for subjects transitioning from capsules to the FDC tablet.

SECTION 4.0, INVESTIGATIONAL PLAN:

Section 4.1.3: Explanation of transition from capsules to the FDC tablet given for subjects ongoing in the Dose Escalation Stage or Dose Confirmation Stage.

SECTION 7.0, STUDY TREATMENTS:

Section 7.3: 3rd paragraph: Clarification made that dose reductions are recommended to be done in consultation with the Astex medical monitor.

Section 7.3: 4th paragraph: language added to indicate that dose reductions for subjects who transition from capsules to the ASTX727 tablet should follow the FDC dose reduction recommendations (ie, reducing the number of dosing days).

SECTION 9.0, STUDY ASSESSMENTS AND PROCEDURES:

Table 3**:** Dosing schedule added for transition from capsules to FDC tablet.

SECTION 11.0, STATISTICS:

Section 11.4: Statement added to describe disposition analysis for subjects who transition from capsules to the FDC tablet.