Official Title:	**A Phase 3, Randomized, Open-Label, Crossover Study of ASTX727 (Cedazuridine and Decitabine Fixed-Dose Combination) versus IV Decitabine in Subjects with Myelodysplastic Syndromes (MDS) and Chronic Myelomonocytic Leukemia (CMML)**
NCT Number:	NCT03306264
Document Dates:	SAP Version 1.0: 27 February 2019

16.1.9 Documentation of Statistical Methods

Statistical Analysis Plan Version 1.0 (27 February 2019)

[redacted]

[redacted]

ASTX727-02

Statistical Analysis Plan

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

Version : Final 1.0

Date: 27 February 2019

Based on: Protocol Version 1.0, dated 06 September 2017

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ABBREVIATIONS AND DEFINITIONS

ADaM	Aanalysis Data Model
AE	adverse event
AML	acute myeloid leukemia
ANOVA	analysis of variance
AUC	area under the curve
BM	bone marrow
BSA	body surface area
CCSP	Cardiac Clinical Statistical Plan
CDA	cytidine deaminase
CI	confidence interval
CMML	chronic myelomonocytic leukemia
CR	complete response
CRF	case report form/electronic case report form
CTCAE	Common Terminology Criteria for Adverse Events
DNA	deoxyribonucleic acid
DNMT	DNA methyltransferase
ECG	electrocardiogram
ECHO/MUGA	Echocardiogram / Multigated Acquisition
ECOG	Eastern Cooperative Oncology Group
ERT	eResearch Technologies, Inc.
FDA	Food and Drug Administration
FDC	fixed-dose combination
GI	gastrointestinal
HI	hematological improvement
HI-E	erythroid response
HI-N	neutrophil response
HI-P	platelet response
HMA	hypomethylating agent
IB	Investigator Brochure
IPD	important protocol deviations
IPSS	International Prognostic Scoring System
IV	intravenous
IWG	International Working Group
LINE-1	long interspersed nucleotide elements-1
mCR	marrow complete response
MDS	myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
NCE	new chemical entity
NE	non-evaluable
NR	non-responder
OR	overall response
OS	overall survival
PAP	Pharmacometric Analysis Plan
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)

PR	partial response
PT	preferred term
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SOC	system organ class
TD	transfusion dependence
TEAE	treatment emergent adverse event
TI	transfusion independence
TLFs	Tables, Listings and Figures
WHO	World Health Organization

1.0 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on the ASTX727-02 protocol (dated 06 September 2017). It details the methodology to be used in analyzing the data and outlines the specifications for data to be included in the Tables, Listings and Figures (TLFs). The analyses specified in this document supersede the high-level analysis plan described in the protocol. Analyses and statistical reporting for ASTX727-02, with the exception of the analyses that are described in a separate Pharmacometric Analysis Plan (PAP) and a separate Cardiac Clinical Statistical Plan (CCSP), will be conducted by Astex Pharmaceuticals Biostatistics department using SAS version 9.4 or higher. Pharmacokinetics (PK) analyses of plasma decitabine, cedazuridine, and cedazuridine-epimer are described in the PAP and will be conducted by pharmacokinetic specialists and statisticians at Certara Strategic Consulting. Analyses of ECG data and exposure vs. QTc Interval assessment are described in the CCSP and will be conducted by expert cardiologists and statisticians at eResearch Technologies, Inc. (ERT).

1.1 Myelodysplastic Syndromes

Myelodysplastic syndromes (MDS) are a heterogenous 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 one-third of patients (Shukron et al 2012).

MDS 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 Treatment Options

Hypomethylating agents (HMAs), such as decitabine and azacitidine, are effective treatment modalities for hematologic cancers and are FDA-approved for higher risk MDS and chronic myelomonocytic leukemia (CMML). HMAs have also shown promising clinical activity in AML. Consecutive daily dosing for 5 or 7 days in 28-day cycles are the approved schedules. Continued

monthly treatment for patients who respond is now the standard of care to avoid early relapse (Cabrero et al 2015). Treatment, which may continue for several months or even years, may engender significant hardship due to the 5 to 7 daily visits required each month, and the 1-hour intravenous (IV) infusion or large-volume subcutaneous injections. A possible consequence is non-compliance or premature discontinuation. Development of a formulation for oral administration of HMAs has proven difficult due to rapid metabolism by cytidine deaminase (CDA) during passage through the gastrointestinal (GI) mucosa and liver. To achieve even modest exposures of drug requires administration of large doses, which are associated with Grades 3 and 4 GI toxicity (nausea, vomiting, and diarrhea) and high variability in exposures (Garcia-Manero et al 2011). Successful development of an oral HMA will ease the burden of long-duration parenteral therapy, particularly for those patients who may benefit most.

1.2.1 ASTX727

Astex Pharmaceuticals is developing an oral drug product, ASTX727, which is composed of the new chemical entity (NCE) cedazuridine (E7727), a CDA inhibitor (Ferraris et al 2014), and decitabine. In animal models, dose-dependent increases in decitabine exposures were achieved when increasing doses of cedazuridine were administered with oral decitabine (refer to the ASTX727 Investigator Brochure [IB]). This interaction effect was demonstrated in CD2F1 mice, rhesus monkeys, and in cynomolgus monkeys, supporting the mechanism of action of improved pharmacokinetics (PK) for the combination of cedazuridine with oral decitabine. Because cedazuridine inhibits CDA in the gut and liver, ASTX727 reduces first pass metabolism of decitabine thus enhancing the bioavailability of decitabine and achieving exposure and hypomethylation activity similar to IV decitabine at the currently approved dosing schedule of 20 mg/m^2 Daily×5.

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

The Astex ASTX727 program's Phase 1-2 first-in-human trial, ASTX727-01, is a PK-guided dose escalation and dose confirmation study of ASTX727 in patients with MDS and CMML intended to define appropriate doses of the individual components of ASTX727 (cedazuridine + decitabine) so that decitabine exposure after oral administration of ASTX727 is comparable to exposure after IV decitabine at the approved daily dose of a 1-hour infusion at 20 mg/m^2. Preliminary results show that ASTX727 enables therapeutic dose-dependent increases in decitabine exposure to therapeutic levels and achieves demethylation and clinical activity comparable to IV decitabine at the FDA approved 5-day dose regimen using fixed doses of 35 mg decitabine and 100 mg cedazuridine (Garcia-Manero 2016, Dacogen Prescribing Information 2014).

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

2.0 STUDY OBJECTIVES

2.1 Primary Objective

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

2.2 Secondary Objectives

- To assess long-term safety and efficacy (response rate) of ASTX727.
- To assess LINE-1 demethylation.
- To assess additional PK parameters.

3.0 STUDY DESIGN

3.1 Overall Study Design

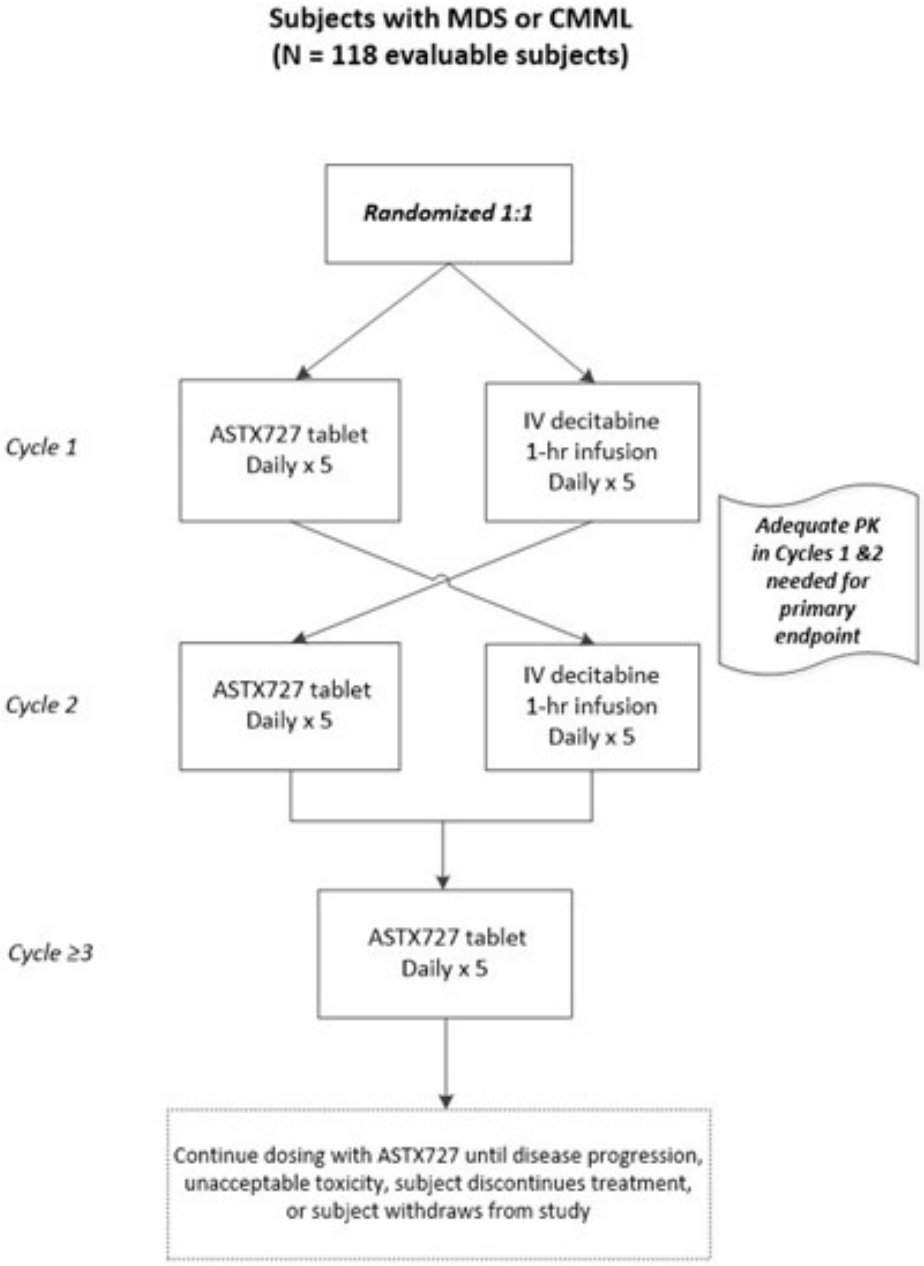
This is a Phase 3, multicenter, randomized, open-label, 2-period, 2-sequence crossover study comparing decitabine AUC equivalence of ASTX727 and IV decitabine. Adult subjects with MDS or CMML who are candidates to receive decitabine will be randomized in a 1:1 ratio to receive the ASTX727 fixed-dose combination (FDC) tablet Daily×5 in Cycle 1, followed by IV decitabine 20 mg/m^2 Daily×5 in Cycle 2, or the converse order (Figure 1). Adequate PK assessments from Cycles 1 and 2 will be required for subjects to be evaluable for analysis of the primary endpoint.

The dosing regimen for this study is shown in Table 1. Subjects will receive the ASTX727 FDC tablet Daily×5 in Cycle 1, followed by a 1-hour infusion of IV decitabine 20 mg/m^2 Daily×5 in Cycle 2, or the converse order. In Cycles ≥3, subjects will receive the ASTX727 FDC tablet Daily×5 in 28-day cycles. After completion of the 2 treatment cycles, subjects will continue to receive treatment with ASTX727 in 28-day cycles until disease progression, unacceptable toxicity, or the subject decides to discontinue treatment or withdraw from the study.

Table 1: Dosing Schedule by Day and Cycle

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

Figure 1: Study Schema



3.2 Study Endpoints

3.2.1 Primary Endpoint

Comparison between ASTX727 and IV decitabine: total 5-day AUC_{0-24} exposures of decitabine after treatment with ASTX727 versus IV decitabine.

3.2.2 Secondary Endpoints

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

4.0 SAMPLE SIZE

The sample size calculation for this study was based on preliminary analysis of 5-day AUC in study ASTX727-01, which showed an estimate of intra-subject CV of 0.5. A conservative CV value of 0.55 was chosen to calculate the sample size.

A total of 118 subjects in the Primary Endpoint PK Analysis Set (Section 5.5) included in the 2 one-sided equivalence tests for the geometric mean ratio of ASTX727 5-day AUC relative to IV decitabine 5-day AUC will provide 90% power at the statistical significance level of 0.05, when the true ratio of geometric means is 1.0, the CV under an unlogged scale is 0.55, and the 90% CI equivalence limits for the ratio of geometric means are 0.8 and 1.25. Assuming 10% of subjects may not be evaluable in the study, approximately 132 subjects will need to be randomized.

5.0 ANALYSIS SETS

5.1 All Subject Analysis Set

The **All Subject Analysis Set** will include information from all screened subjects, including those who did not meet the study entry criteria. This data set will be used only for screening displays.

5.2 Randomized Subject Analysis Set

The Randomized Subject Analysis Set will include data from all subjects who were randomized into the study. Subjects will be included in the treatment group according to their randomly assigned treatment.

5.3 Efficacy Analysis Set

The Efficacy Analysis Set will include data from all subjects who received any amount of study treatment. All data will be included, and no subjects excluded because of protocol deviations. Subjects will be included in the treatment sequence according to their randomly assigned treatment sequence.

5.4 Safety Analysis Set

The Safety Analysis Set includes data from all subjects who received any amount of study treatment. In the safety analysis, no data exclusion will be allowed because of protocol deviations. Subjects will be included in the treatment sequence according to the treatment sequence received.

5.5 Pharmacokinetics Analysis Set

The details of PK analysis sets are covered under a separate Pharmacometric Analysis Plan (PAP) document.

5.6 Pharmacodynamic Analysis Set

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

6.0 SCHEDULE OF ANALYSES

Two formal analyses are planned for this study:

The first analysis will be performed after all evaluable subjects have completed Cycles 1 and 2 and will include analyses of all PK endpoints, maximum %LINE-1 demethylation, and all available safety and clinical response rate data up to the data cutoff date for the first analysis.

A second analysis will be performed after all subjects have completed 6 months of follow-up or permanently discontinued treatment prior to 6 months of follow up from their first treatment dose. Comprehensive analyses of all efficacy (response rate, transfusion independence, leukemia-free survival, and overall survival), and safety will be performed using all available data up to the data cutoff for the second analysis.

No formal interim analyses are planned for this study.

7.0 STATISTICAL ANALYSIS

Unless otherwise specified, all statistical tests and confidence intervals (CIs) described in this document will be two-sided with alpha = .05. The SAS® statistical package (version 9.4 or a later version) will be used for the analyses.

The first dosing date is defined as the first date the subject received any study treatment. Subject disposition, demographics, and baseline characteristics will be summarized by treatment sequence and all subjects combined (Total). Adverse events (AEs) will be summarized by actual treatment received at the onset of the AE (Section 7.6.2). Efficacy analyses, laboratory tests, vital signs, ECG, and ECOG performance status will be summarized by treatment sequence and all subjects combined (Total), unless otherwise specified.

The following data listings by study center and subject ID will be provided: screened subjects (with reason for screen failure), disposition (with reasons for discontinuation of treatment and withdrawal from study), important protocol deviations, demographic and baseline characteristics, study drug administration, individual efficacy data, subjects excluded from the efficacy analysis, AEs, all deaths (including primary cause of death), serious adverse events (SAEs), other significant AEs (including treatment discontinuation due to AEs), concomitant medications, and the protocol specified laboratory measurements. Additional data listings may be generated to support other relevant discussions in Clinical Study Report.

7.1 Subject Disposition

Subject disposition including number of subjects randomized (enrolled), treated, and treatment discontinuation by reason, as well as reasons for withdrawal from study (ie, death, complete consent withdrawal, or lost to follow-up) and subjects ongoing at data-cut will be summarized using frequencies and percentages based on information collected on the study case report form pages. Subjects in the Randomized Subject Analysis Set will be included in the disposition analysis. A separate screening summary, based on the All Subjects Analysis Set, will include the number of subjects who were screened, failed screening and the reasons for screen failure.

7.2 Demographic and Other Baseline Characteristics

The Randomized Subject Analysis Set (Section 5.2) will be used to summarize demographic and baseline characteristics. The demographic variables consist of age, age category (<18, 18-64, 65-84, ≥85 years), sex, ethnicity, race, and country. Baseline characteristics include height, weight, BSA, ECOG performance status, prior anticancer therapy if any including prior HMA treatment (decitabine or azacitidine), study disease (MDS or CMML), IPSS risk category, time since diagnosis, cytogenetic risk classification, disease pathology (eg, hemoglobin, neutrophils, platelets, bone marrow [BM] blast counts (%), peripheral blood blast counts), transfusion dependence (RBC and platelet). Race and ethnicity summaries will be based on the levels according CDISC standards.

Baseline values are the last value collected before or on the 1st dosing date unless otherwise specified.

Time since diagnosis will be calculated as the (date of 1st dose – date of diagnosis). If the day is missing for date of diagnosis, the 15th of the month is used. If the month is missing, July 1st is used. If the year is missing, the date is left as missing.

Subject demographic and baseline characteristics will be summarized by mean, standard deviation, median, minimum, and maximum for continuous variables; and by counts and percentages for categorical variables.

7.3 Pharmacokinetics Analyses

The primary endpoint analysis includes data from the following PK assessment days to calculate the 5-day total cycle AUC:

- ASTX727 $AUC_{0\text{-}24}$: Days 1, 2, and/or 5.
- IV decitabine $AUC_{0\text{-}24}$: Days 1 and/or 5.

All details regarding the analyses of the primary and secondary PK endpoints are provided in a separate PAP.

7.4 Pharmacodynamic (LINE-1) Analyses

The PD (LINE-1) Analysis Set (Section 5.6) will be used for analyses of LINE-1 methylation. Since LINE-1 methylation levels often do not completely return to baseline by Day 28 of Cycle 1, and to avoid the confounding effects of differing baselines in Cycle 2 vs Cycle 1, subjects will be compared for each of the 2 cycles separately using the baseline values prior to each cycle, thus limiting the evaluation to interpatient comparisons in each of the 2 cycles.

For each of Cycles 1 and 2, LINE-1 methylation data will be summarized descriptively (using mean, standard deviation, standard error, median, minimum and maximum) by visit and treatment. Descriptive statistics for maximum %LINE-1 demethylation will be summarized by treatment.

In addition, the 95% CIs for mean maximum %LINE-1 demethylation in Cycles 1 and 2 will be provided for ASTX727 and IV decitabine, respectively. The 95% CI for the difference in mean maximum %LINE-1 demethylation between ASTX727 and IV decitabine in Cycles 1 and 2 will also be generated based on an analysis of variance (ANOVA) model with treatment as factor.

7.5 Efficacy Variables and Analyses

Efficacy analyses will be based on the Efficacy Analysis Set (Section 5.3). Efficacy variables will be summarized using descriptive statistics and there will be no comparison analyses between treatment sequences.

7.5.1 Response Rate

The evaluation of response (Table 2) is based on IWG 2006 MDS Response Criteria (Cheson et al 2006) and conducted by medical review of peripheral blood, bone marrow, and transfusion data.

Table 2: IWG 2006 MDS Response Criteria

Complete Response (CR): the following for 4 weeks		
Peripheral: Normal peripheral counts with persistent granulocyte count ≥1.0×10^9/L, platelet ≥100×10^9/L and Hgb ≥11 g/dL. No blasts.		
Marrow: Normal bone marrow with persistent marrow blasts ≤5%. Persistent dysplasia will be noted.		
Partial Response (PR): the following for 4 weeks		
Peripheral: Normal peripheral counts with granulocyte count ≥1.0×10^9/L, platelet count ≥100×10^9/L, and Hgb ≥11 g/dL. No blasts.		
Marrow: Normal bone marrow and marrow blasts >5%, but were reduced by 50% or more.		
Marrow Complete Response (mCR): the following for 4 weeks		
Reduction of bone marrow blasts to ≤5% and decrease by 50% or more without normalization of peripheral counts.		
Hematological Improvement (HI): lasts at least 8 weeks		
Erythroid Response (HI-E):	Major Response:	Hemoglobin increase ≥1.5 g/dL in the absence of RBC transfusion.
Platelet Response (HI-P):	Major Response:	Absolute increase of platelet count from <20 to >20×10^9/L and by at least 100%, or if more than 20×10^9/L, by an absolute increase of at least 30×10^9/L in the absence of platelet transfusion.
Neutrophil Response (HI-N):	Major Response:	Granulocyte increase ≥100%, and by an absolute increase ≥0.5×10^9/L.

The details of the response criteria are presented in (Cheson et al 2006).

Response categories listed in Table 2, as well as the start and stop date of a subject's best response (CR, PR, mCR, and HI) will be determined by medical review. Baseline values of neutrophils, hemoglobin and platelets used for response evaluation are the average of all values obtained during screening up to and including the first dosing date. If there is only one value available before treatment then it will be used as the baseline value.

The following rates of best response will be estimated using sample proportions and 95% Wald CI based on the number of subjects in the Efficacy Analysis Set:

- CR.
- PR.
- mCR.
- HI (HI-E, HI-P or HI-N).
    - HI-E.
    - HI-P.

- HI-N.

- Overall response (OR [CR+PR+mCR+HI]).
- mCR with HI.

Subjects with these different response categories, as well as non-responders (NR) and non-evaluable (NE) subjects will be listed and summarized using frequency counts and proportion of subjects with each category of best response (each subject will be counted once with best response, in the following hierarchy: CR, followed by PR, followed by mCR, followed by HI). In the HI category, subjects will be listed in each HI category they achieved, so subjects may be counted under multiple HI categories). The category of mCR with HI is a subset of mCR subjects who also achieved HI. Subjects who did not have a valid post-treatment efficacy assessment will be classified as NE for response classifications. These subjects will be included in the denominator of the efficacy analysis for calculation of different response rates.

For the first analysis (see Section 6.0), the responses will be summarized for all subjects regardless of the length of follow-up at the time of the data cutoff date. Response will also be summarized based on the subjects with mature response data from those subjects in the Efficacy Analysis Set who have completed at least 6 months of follow-up or who have permanently discontinued treatment prior to 6 months of follow up from their first treatment dose.

For the second analysis (see Section 6.0), duration of best response (CR, PR, and mCR) will be summarized.

7.5.2 Transfusion Independence

Transfusion independence (TI) will be analyzed separately for platelet and RBC transfusions. Transfusion dependence (TD) and transfusion independence are defined as follows:

- Transfusion dependence at baseline: documentation of 2 units or more of transfusion within 56 days of the first dose of study treatment.
- Post-treatment transfusion independence: no transfusion for 56 consecutive days or more after the first dose of study treatment while maintaining hemoglobin ≥8 g/dL (RBC TI) or maintaining platelets $\geq 20 \times 10^9$/L (Platelet TI).

Post-treatment transfusion independence rate will be calculated separately for RBC transfusion independence and platelet transfusion independence as the number of subjects who are transfusion independent post treatment (n) among those who were transfusion dependent at baseline (N). The 95% Wald CI for transfusion independence rates will be provided. The same analyses will be performed for 84-day and 112-day transfusion independence, defined as no transfusion for 84 consecutive and 112 consecutive days, respectively, while maintaining hemoglobin ≥8 g/dL (RBC TI) or maintaining platelets $\geq 20 \times 10^9$/L (Platelet TI).

7.5.3 Leukemia-Free Survival

Leukemia-free survival is defined as the number of days from the date of randomization to the date of MDS progression to AML or death.

The date of MDS progression to AML or death will be defined based on the earliest date of following:

- Death date.
- AML conversion date defined as the earliest date of the following:
  - AML conversion date on the Conversion to AML CRF page.
  - The first date when a record of ≥20% blasts in bone marrow was reported or 2 consecutive records of ≥20% blasts in peripheral blood were reported.

Subjects who have bone marrow or peripheral blood blasts ≥20% at baseline will be censored at the date of randomization, and subjects without a time to AML event as described above will be censored on the date of last contact.

The Kaplan-Meier plot will be provided based on the Efficacy Analysis Set. Estimated median leukemia-free survival and 95% CIs will also be provided if available.

7.5.4 Overall Survival

Overall survival is defined as the number of days from the date the subject was randomized to the date of death (regardless of cause). Subjects without documentation of death will be censored on the last date of contact or the last date subject was confirmed alive on the Study Discontinuation CRF page, whichever is later.

The Kaplan-Meier plot will be provided based on the Efficacy Analysis Set. Estimated median survival time (days) and 95% CIs will also be provided if available. In addition, subject follow-up time in days will also be summarized.

7.6 Safety Variables and Analyses

Safety Analysis will be performed using the Safety Analysis Set (Section 5.4). Safety was assessed by subject-reported and investigator-observed adverse events (AEs), along with physical examination, clinical laboratory tests (hematology, chemistries and urinalysis), vital signs,

concomitant medications, ECOG performance status and ECGs. Exposure to study treatment, deaths, and causes of deaths will be tabulated.

7.6.1 Study Treatment and Exposure

The number of cycles completed or partially completed per subject will be summarized using descriptive statistics. Frequency count and percentage of dose delayed cycles and dose reduced cycles reported by the investigator will be summarized at the subject level and cycle level.

7.6.2 Adverse Events

Adverse events 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 Medical Dictionary for Regulatory Activities (MedDRA). Severity of AEs will be graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Treatment-emergent AEs (TEAEs) are defined as events that first occurred or worsened on or after the date of the first dose of study treatment until 30 days after the last dose of study treatment or until the start of a post-treatment alternative anti-cancer treatment for MDS/ CMML and subsequent AML, whichever occurs first, with the following exceptions: events that occurred after 30 days beyond the last dose of study treatment or the start of a post-treatment alternative anti-cancer treatment for MDS/CMML and subsequent AML will also be considered treatment-emergent if the events are both serious and related to the study treatment. For the purpose of determining whether an AE is a treatment-emergent AE, incomplete AE start and stop dates will be imputed conservatively following the data programming standards as detailed in the Aanalysis Data Model (ADaM) data reviewer guide.

All AE data collected in the study database with an AE start date on or before the data cutoff date will be included in the data listings, including those that are not treatment emergent. Only TEAEs will be included in the AE summary tables.

An overall safety summary table containing counts and percentages of subjects with any AE, any AE Grade ≥3, AE leading to treatment discontinuation, any SAE, and subcategories of SAEs (death vs not death) will be produced.

Related events are those that the Investigator considered to be related to study treatment as described in the study protocol. All summaries of AEs will be made separately in the following groups:

- IV decitabine in Cycle 1 or Cycle 2.
- ASTX727 in Cycle 1 or Cycle 2.
- ASTX727 in Cycle 3 or later.
- Total for ASTX727.

- Total for Phase 3.

The number and percentage of subjects experiencing AEs will be summarized by MedDRA SOCs (sorted alphabetically) with PTs sorted alphabetically within each SOC. The number and percentage of subjects experiencing AEs will also be summarized by PT and sorted by event frequency of the Total for ASTX727 column. Related AEs, serious AEs (SAEs), and related SAEs will be summarized similarly. A summary of AEs with fatal outcome, AEs resulting in permanent treatment discontinuation, and AEs resulting in treatment delay or dose reduction will also be provided. Additional summaries will be generated by SOC, PT and CTCAE grade. For these summaries, if the occurrence of a particular AE for a given subject is reported more than once, the event is only counted once with its worst CTCAE grade.

7.6.3 Concomitant Medications

Concomitant medications are medications taken with a start date on or after the date of the first dose of study treatment, or those with a start date before the start of the administration of study treatment and a stop date on or after the start of the administration of study treatment. Medications taken beyond 30 days from the last dose of study treatment or after the start of a post-treatment alternative anti-cancer treatment for MDS/CMML and subsequent AML are not considered concomitant medications, unless they are used for treating a related SAE. For the purpose of inclusion in the concomitant medication tables, incomplete medication start and stop dates will be imputed conservatively.

Concomitant medication will be coded by the latest version of WHO Drug Dictionary before the data download and summarized by Anatomical Therapeutic Chemical (ATC level 2) and drug name, sorted alphabetically, using counts and percentages.

Special interest concomitant medications include anti-emetic drugs, growth factors (including G-CSF, GM-CSF and ESAs), anti-infective medications (including but not limited to anti-bacterials, anti-mycotics, anti-mycobacterials, anti-virals and immunoglobulins) and hydroxyurea given to reduce high counts during study treatment and not as part of a subsequent anti-leukemia treatment. These concomitant medications will be tabulated separately.

7.6.4 Laboratory Tests

Laboratory values will also be graded, if possible, by CTCAE v4.03 in conjunction with the Harrison (18th edition) lab book normal values (Longo et al 2011). Shift tables will display (1) shift from baseline grade to the worst grade during the study, and (2) shift from baseline grade to the last grade at the end of study.

Laboratory values recorded as an interval such as "≥x", "<x", or "2+" will be handled, if necessary for calculation purposes, following the data programming standards as detailed in the ADaM data reviewer guide.

7.6.5 Vital Signs

Vital signs will be summarized by visit and treatment group using proportion of subjects with each vital sign being too high or too low according to conventionally accepted vital sign normal ranges as follows:

- Pulse rate 110 bpm or greater.
- Pulse rate 50 bpm or less.
- Diastolic blood pressure 110 mmHg or greater.
- Diastolic blood pressure 55 mmHg or less.
- Systolic blood pressure 180 mmHg or greater.
- Systolic blood pressure 80 mmHg or less.
- Respiration rate 20 breaths/min or greater.
- Body temperature 39°C or greater.

7.6.6 Electrocardiogram (ECG)

The ECG data will be summarized and presented as part of a separate more extensive analysis that will explore the relationship between the change from baseline in QTc intervals and plasma concentrations of ASTX727 or IV decitabine. Further details regarding the analyses of the ECG data will be provided in the CCSP.

7.6.7 ECOG Performance Status

Shift tables for ECOG from baseline to the worst grade, and from the baseline to the last available grade will be provided.

7.6.8 Echocardiogram / Multigated Acquisition (ECHO/MUGA)

This was only done at baseline for reference. Data will be preserved in a Study Data Tabulation Model (SDTM) dataset. No particular analysis will be conducted.

7.6.9 Physical Examination

Physical examination data will be preserved in a SDTM dataset. No particular analysis will be conducted.

7.7 Handling of Missing Data and Other Data Anomalies

No missing data imputations are planned for the study, except as specified. Subjects lost to follow-up will be included in statistical analyses to the point of the data cut-off date.

7.8 Handling of Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team and updated during the IPD reviews throughout the study prior to data cut-off date. IPD will be tabulated by IPD category and listed by subject. Non-important protocol deviation data will be preserved in a SDTM dataset. No particular analysis will be conducted.

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