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), Chronic Myelomonocytic Leukemia (CMML), and Acute Myeloid Leukemia (AML)**
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16.1.9 Statistical Analysis Plan

Statistical Analysis Plan (for AML) version 2.0 (15 October 2021)

ASTX727-02

Statistical Analysis Plan (for AML)

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), Chronic Myelomonocytic Leukemia (CMML), and Acute Myeloid Leukemia (AML)

Version: 2.0

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VERSION HISTORY

SAP Version	Approval Date	Change	Rationale
1	12JUL2021	Not Applicable	Protocol Amendment 2.6 Europe, dated 27 January 2021
2		Reponse Critreria	Protocol Amendment 2.7 Canada, dated 08 March 2021; the original IWG 2003 criteria and ELN 2017 criteria for AML response assessment

ABBREVIATIONS AND DEFINITIONS

ADaM	Analysis 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
CRh	complete response with partial hematologic recovery
CRi	CR with incomplete blood count recovery
CRp	CR with incomplete platelet recovery
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
EFS	event-free survival
ERT	eResearch Technologies, Inc.
FAB	French American British
FDA	Food and Drug Administration
FDC	fixed-dose combination
GI	gastrointestinal
HCT	hematopoietic cell transplantation
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
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
PB	peripheral blood
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
SEER	US Surveillance, Epidemiology and End Results
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

Study ASTX727-02 originally included only myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML) subjects. The Amendment 1.3 Europe (10 December 2018) expanded the subject population to include ~70 acute myeloid leukemia (AML) evaluable subjects in Europe to obtain pharmacokinetic data in the AML population to allow the PK-bridging approach for marketing approval in the EU. This Statistical Analysis Plan (SAP), which is based on the ASTX727-02 protocol amendment 2.6 Europe (dated 27 January 2021), will only describe analysis of AML subjects included in the ASTX727-02 study (ASTX727-02 SAP [AML]). There is a separate SAP which has been approved eaerlier for analysis of only MDS/CMML subjects included in the ASTX727-02 study (ASTX727-02 SAP). The ASTX727-02 SAP (AML) details the methodology to be used in analyzing the AML subject data and outlines the specifications for data to be included in the Tables, Listings and Figures (TLFs) of the Clinical Study Report for AML subjects. The analyses specified in this document supersede the high-level analysis plan described in the protocol. Analyses and statistical reporting for ASTX727-02 AML subjects, with the exception of the analyses that are described in a separate Pharmacometric Analysis Plan (PAP) and a separate Cardiac Clinical Statistical Plan (CCSP) for AML subjects, 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 Acute Myeloid Leukemia

In a recent analysis of US Surveillance, Epidemiology and End Results (SEER) data, AML trends in relative survival by age were compared over 3 successive decades from 1977 through 2006 for 19,000 patients at least 65 years of age with AML (Thein et al 2013). Overall, survival improved for each successive decade in patients from 65 to 74 years old. In this age range, 12-month survival increased from 20% to 25%-30% in the 3 successive cohorts. However, survival rates did not significantly improve in patients ≥75 years of age.

The oldest patients (85 or more years of age) have the lowest survival; older AML patients are more likely to have poor-risk cytogenetic abnormalities, which are associated with lower complete remission rates. In addition, elderly patients may have comorbid illnesses, poor performance status, or diminished organ function, any of which can impair their ability to tolerate antileukemic therapy (Cashen et al 2010). Thus, despite ongoing incremental improvements in both AML chemotherapy and supportive care since the mid-1970s, mortality following an AML diagnosis remains persistently high and with minimal improvement in elderly patients.

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 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 has developed an oral drug product, ASTX727 (recently approved as INQOVI® [current INQOVI Prescribing Information]), which is composed of the new chemical entity (NCE) cedazuridine (E7727; 100 mg), a CDA inhibitor (Ferraris et al 2014), and 35 mg decitabine. In animal models, dose-dependent increases in decitabine exposures were achieved when increasing doses of cedazuridine were administered with oral decitabine (refer to the ASTX727 Investigator Brochure [IB]). This interaction effect was demonstrated in CD2F1 mice, rhesus monkeys, and in cynomolgus monkeys, supporting the mechanism of action of improved pharmacokinetics (PK) for the combination of cedazuridine with oral decitabine. Because cedazuridine inhibits CDA in the gut and liver, ASTX727 reduces first pass metabolism of decitabine thus enhancing the bioavailability of decitabine and achieving exposure and hypomethylation activity similar to IV decitabine at the currently approved dosing schedule of 20 mg/m^2 Daily×5. Decitabine was approved in 2006 by the United States Food and Drug Administration (US FDA) as Dacogen® (decitabine) (current Dacogen Prescribing Information), administered as a 1-hour IV infusion for the treatment of higher risk patients with MDS and CMML. Dacogen was also approved by the EMA in 2012 for treatment of adult patients with AML who are not candidates for intensive chemotherapy (current Dacogen Summary of Product Characteristics).

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

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

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

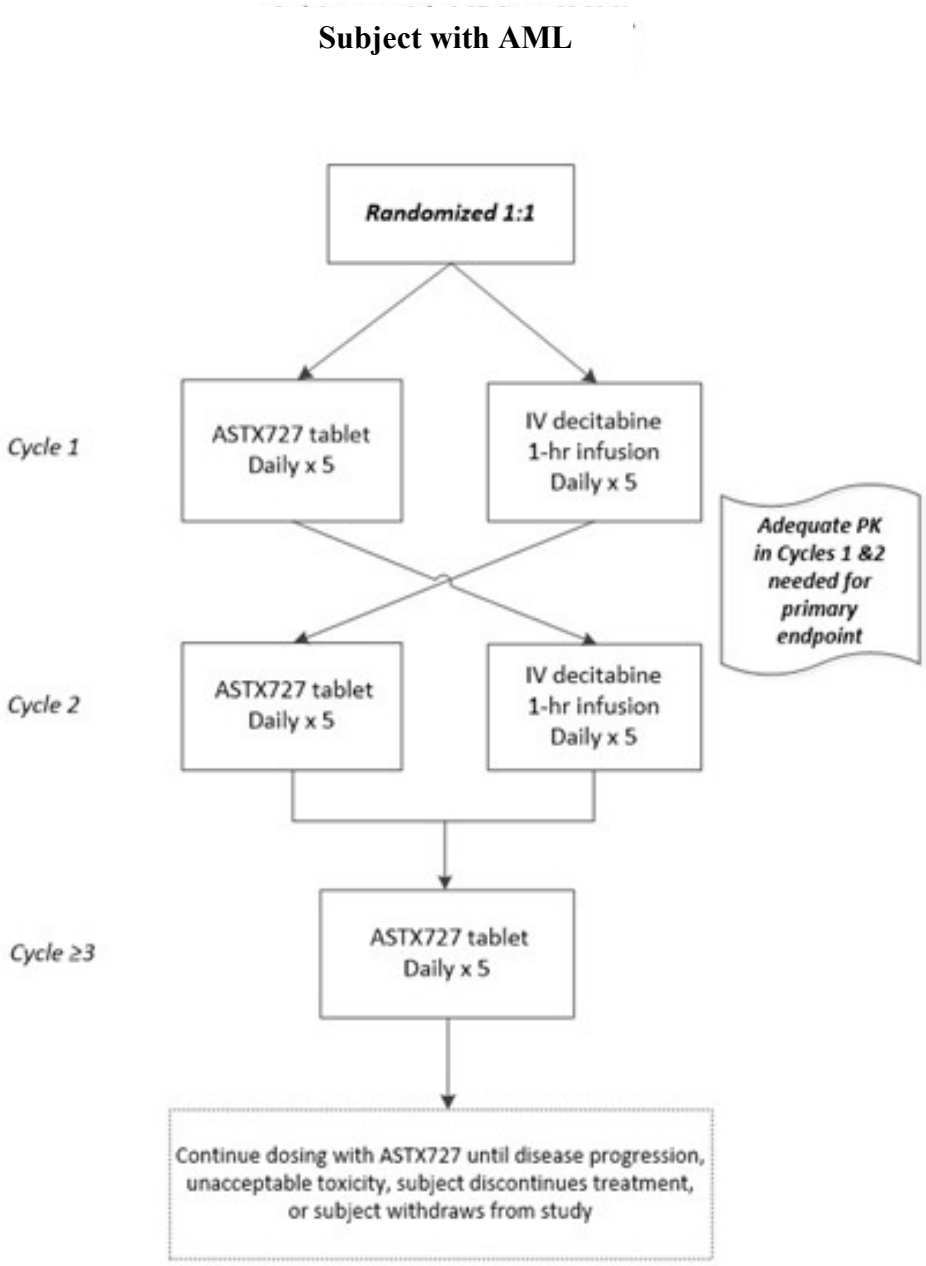
This is a Phase 3, multicenter, randomized, open-label, 2-period, 2-sequence crossover study comparing decitabine AUC equivalence of ASTX727 and IV decitabine. Adult subjects with MDS, CMML, or AML who are candidates to receive IV decitabine will be randomized in a 1:1 ratio to receive the ASTX727 FDC tablet Daily×5 in Cycle 1, followed by IV decitabine 20 mg/m^2 Daily×5 in Cycle 2, or the converse order (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**					
Cycle Day	**1**	**2**	**3**	**4**	**5**	**6-28**	**1**	**2**	**3**	**4**	**5**	**6-28**	**1**	**2**	**3**	**4**	**5**	**6-28**
If randomized to ASTX727 in Cycle 1, then:																		
ASTX727 tablet	×	×	×	×	×								×	×	×	×	×	
IV decitabine (20 mg/m^2)							×	×	×	×	×							
If randomized to IV decitabine in Cycle 1, then:																		
ASTX727 tablet							×	×	×	×	×		×	×	×	×	×	
IV decitabine (20 mg/m^2)	×	×	×	×	×													

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], CR with incomplete platelet recovery [CRp], and CR with incomplete blood count recovery [CRi] based on modified IWG 2003 AML response criteria (Cheson et al 2003) and as in the DACO-016 study (ie, CRp as a subset of CRi) (Kantarjian et al 2012). In addition, complete response with partial hematologic recovery (CRh) will also be assessed. CRh will be reported as in Kantarjian et al 2017 and as used in DiNardo et al 2020.
- Time to first response, time to best response, and time to CR.
- Duration of CR and duration of combined CR and CRh, defined respectively as the time interval from the first CR to time of relapse and the time interval from the first CR or CRh to time of relapse.
- Red blood cell (RBC) or platelet transfusion independence (TI).
- Overall survival (OS), defined as the number of days from the date of randomization to the date of death from any cause.
- Survival rates at 6 months, one year, and two years.
- Event-free survival (EFS), defined as the number of days from the date of randomization to the date of treatment failure or death from any cause, whichever occurs first.
- Progression-free survival (PFS), defined as the number of days from the date of randomization to the date disease progression or death from cause, witchever occurs first.

4.0 SAMPLE SIZE

In an equivalence test of mean using two one-sided tests on data from a two-by-two crossover design, a total sample size of ~70 evaluable subjects achieves 90% power at a 5% significance level when the true ratio of the means is 1.0, the coefficient of variation on the original, unlogged scale is 0.41, and the equivalence limits of the mean ratio are 0.80 and 1.25. Assuming ~20% of subjects may not be evaluable in the study, approximately 85 subjects will need to be randomized.

The estimated intra-subject CV from analysis of 5-day AUC in study ASTX727-02 with MDS and CMML subjects was approximately 0.32. A conservative intra-subject CV value of 0.41 was used above for AML sample size justification.

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 pharmacodynamic (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

The analysis for submission purpose 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. All available data up to the data cutoff will be included in this analysis. An additional analysis may be conducted when all subjects have completed the study. 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, and race. Baseline characteristics include height, weight, body

surface area (BSA), ECOG performance status, prior anticancer therapy if any including prior HMA treatment (decitabine or azacitidine), study disease (De Novo AML or Secondary AML), secondary AML specify (MDS, Other Antecedent Hematological Disorder, Therapy-related AML), FAB classification, time since diagnosis, cytogenetic risk classification, hemoglobin, neutrophils, platelets, bone marrow [BM] blast counts (%), peripheral blood [PB] blast counts), transfusion dependence (RBC and platelet). Race and ethnicity summaries will be based on the levels according to 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. Complete details of imputation rules are presented in the Astex Data Programming Standards.

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 formal comparison analyses between treatment sequences.

7.5.1 Response Rate

The evaluation of response (Table 2) will be based on Modified IWG 2003 AML Response Criteria (Cheson et al 2003), and include CRp according to the DACO-016 study (Kantarjian et al 2012) for that CRp is not any response catergory of IWG 2003 AML Response Criteria (Cheson et al 2003). Subjects who do not have a valid post-treatment efficacy assessment (ie, no post-treatment BM/PB sample or the quality of BM/PB sample is not adequate for an assessment of efficacy) will be classified as not evaluable (NE) for response classifications. Subjects who cannot be classified into a response category (CR, CRi, or PR) or into the NE category will be classified as non-responders (NR). According to the recommendations of the European LeukemiaNet (Döhner et al 2017), progressive disease is defined as >50% increase in marrow blast % from baseline (15% increase in cases with <30% marrow blasts at baseline); or >70% marrow blasts over at least 3 months; or >50% increase in peripheral blasts to $\geq 25 \times 10^9$/L (≥25,000/μL); and stable disease is defined as absence of CR, CR subtype, PR and progressive disease for at least 3 months. CRh, CR with partial hematologic recovery, is defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/μL and ANC >500/μL) (Kantarjian et al 2017). Evaluation of response will be conducted by Astex medical monitors assisted by programmed data listings, as detailed in the Astex AML Response Assessment Criteria (Section 8.1).

Table 2: Modified IWG 2003 AML Response Criteria

Response[a]	ASTX727-02 Specific Criteria
CR	ANC ≥1000/μL, Platelets ≥100,000/μL, independence from RBC and platelet transfusions over the past week, no leukemic blasts[b] <5% leukemic blasts
CRi	All CR criteria except ANC <1000/μL or Platelets <100,000/μL
CRp	All CR criteria except Platelets <100,000/μL and platelet transfusions over the past week
PR	All CR criteria except decrease of ≥50% in leukemic blasts to level of 5% to 25%

ANC=absolute neutrophil count; CR=complete response; CRp=complete response with incomplete platelet recovery; CRi=CR with incomplete blood count recovery; PR=partial response.

[a] Responses are based on both PB and BM conditions.

[b] For the purpose of response assessment and according to published IWG criteria, blasts may be seen in PB as rare PB blasts may be identified during regeneration, but the subject is in CR if BM blasts are <5% with no Auer rods.

Source: Cheson et al 2003; Kantarjian et al 2012

For subjects who experience different response levels at different visits, the best response (see Table 2) will be used for summary and analyses. Overall objective response will be the number of subjects achieving CR, CRi, and PR with each subject counted once according to their best response. CRp, a subcategory of CRi will be listed under CRi. Composite response rates, CR + CRi (either CR or or CRi), CR + CRi + PR (either CR or CRi or PR), CR + CRh (either CR or CRh) and CRh, will also be included in the response analysis.

Subjects with these different response categories will be listed and summarized using frequency counts and proportion of subjects with each category. The 95% Clopper-Pearson confidence interval will be provided for each response rate. Subgroup analyses such as by age category (<75, ≥75) may be performed.

7.5.2 Time to First Response and Time to Best Response

Both time to first response and time to best response will be calculated and analyzed for subjects who achieve a response of CR, CRi (or CRp or CRh), or PR. Time to first response is defined as the time, in days, from the date of first treatment (C1D1) to the first date when any response is achieved. Time to best response is similarly defined as the time, in days, from the date of first treatment (C1D1) to the first date when a subject's best response, in the order of CR, CRi (or CRp or CRh), or PR, is achieved. The times to first response and best response will be summarized using mean, standard deviation, median, minimum, and maximum. Time to CR will be summarized similarly.

7.5.3 Duration of Response

A combined duration of CR and CRh (in number of days) will be calculated from the first time a CR or CRh is observed to the date of the earliest of the following 3 events: (1) relapse (defined as the earliest time point whereby BM assessment or PB assessment by the investigator indicate relapse/disease progression due to confirmed reappearance of leukemic blasts in PB or ≥5% leukemic blasts in BM, or clinical progression determined by the investigator), (2) start of alternative therapy (except hematopoietic cell transplantation [HCT]) or (3) death. In the absence of any event, the combined duration of CR and CRh will be censored at the last available time point (BM assessment, PB assessment, or safety/long-term follow-up visit) at which an event was not observed. Duration of combined CR and CRh will be analyzed using the Kaplan-Meier method for subjects who achieved a CR or CRh during the study; the median and quartiles of the duration, as well as their respective 95% CIs will be provided. Duration of CR or CRp and duration of CR will be calculated and analyzed similarly.

7.5.4 Transfusion Independence

Transfusion independence (TI) will be analyzed separately and simultaneously 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 $\geq 20\times10^9$/L (platelet TI).

Post-treatment transfusion independence rate will be calculated separately and simultaneously 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% Clopper-Pearson 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 $\geq 20\times10^9$/L (platelet TI).

7.5.5 Overall Survival

Overall survival (OS) is defined as the number of days from the date the subject was randomized to the date of death (regardless of cause). In the absence of documented death at the time of anlaysis, the OS time will be censored on the last date the subject is known alive.

The Kaplan-Meier plot will be provided based on the Efficacy Analysis Set. The median (and quartiles) duration of OS and the associated 95% CI will be estimated using the Kaplan-Meier method and the log-log transformation for the survival function. In addition, subject follow-up time in days will also be summarized.

7.5.6 Survival Rate at 6 Months, One Year and Two Years

One-year survival rate is defined as the survival rate at the end of the first year from randomization.

One-year survival rate and the associated 95% CI will be estimated by Kaplan-Meier procedure with the log-log transformation. The survival rates at 6 months and 2 years will be similarly summarized.

7.5.7 Event-Free Survival

Event-free survival (EFS) was not described in the study protocol and was added in this SAP. EFS is defined as the number of days from the date of randomization to the date of treatment failure (disease progression/relapse, discontinue treatment due to disease progression or treatment-related adverse event, or alternative anti-leukemia therapy except for HCT) or death from any cause, whichever occurs first. In the absence of any of these events at the time of analysis, EFS time will be censored on the last date the subject is known alive. Subjects who do not have post-baseline information will be censored at the date of randomization. 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.

7.5.8 Progression-free Survival

Progression-free (PFS) survival was not described in the study protocol and was added in this SAP. PFS is defined as the number of days from the date of randomization to the date of disease progression (including relapse) or death from any cause, whichever occurs first. In the absence of disease progression or death at the time of analysis, PFS time will be censored on the last date the subject is known alive. 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.

7.6 Safety Variables and Analyses

Safety Analysis will be performed using the Safety Analysis Set (Section 5.4). Safety is 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-leukemia treatment, 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-leukemia treatment 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 conventions as detailed in the Astex Data Programming Standards.

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 the AML study.

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-leukemia treatment 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 following the data programming conventions as detailed in the Astex Data Programming Standards.

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 is 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 for response assessment as specified in Section 7.5.1. 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.

8.0 SUPPORTING DOCUMENTATION

8.1 Appendix 1: Astex AML Response Assessment Criteria

AML Response Assessment Criteria

Objective: To establish AML response assessment criteria guidelines to meet industry standards and match pivotal studies

- Document the original IWG 2003 criteria and ELN 2017 criteria for AML response assessment
- Document any criteria language needing clarification and/or study-specific modification(s) from the original criteria along with sufficient justification and supporting references
- Standardize AML response assessment in Astex protocols and BDM table output; and Astex medical adjudication
- Provide sufficient detail for programming to produce desired output
- Review and document annually and be used for protocol development, training purposes, and generation of SAPs

Version Number:	1.0
Version Date:	15 Oct 2021
Replaced Version Number:	N/A
Replaced Version Dated:	N/A

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IWG 2003 AND ELN 2017 AML RESPONSE ASSESSMENT

AML Response Assessment	IWG 2003 AML Response Criteria[1]	ELN 2017 AML Response Criteria[2]	Issues Requiring Clarification(s)	Study-specific Modification(s): ASTX727-02
Complete Remission (CR)	• Morphologic leukemia-free state (MLFS) ➢ <5% blasts in an aspirate sample with marrow spicules and with a count of at least 200 nucleated cells. There should be no blasts with Auer rods. ➢ No residual evidence of extramedullary leukemia (such as CNS or soft tissue involvement). ➢ The presence of a unique phenotype (by flow cytometry) identical to what was found in the pretreatment specimen (eg, CD34, CD7 coexpression) should be viewed as persistence of leukemia. • Hemoglobin concentration or hematocrit has no bearing on remission status, although the patient must be independent of transfusions. • Absence of persistent blasts in the peripheral	• Bone marrow blasts <5% • Absence of circulating blasts and blasts with Auer rods • Absence of extramedullary disease • ANC ≥1.0x10^9/L (1000/uL) • Platelet count ≥100x10^9/L (100,000/uL)	• ≥200 nucleated cells count requirement • Auer rods is a hematopathology determination and not easily collected in EDC • Extramedullary disease is a clinical/radiographic determination and not easily collected in EDC • Flow cytometry data is a hematopathology determination and is not easily collected in EDC • Transfusion independency requirements not specifically defined in IWG 2003 and transfusion independency is not mentioned at all in the ELN 2017 • Presence of rare peripheral blasts may be normal in a regenerative marrow (medical adjudication required) • IWG 2003 ANC requirement is written as “more than” but platelet requirement is written as “≥” for platelet requirement. • “Rare peripheral blast” not defined numerically in IWG 2003 and not mentioned in ELN 2017	The protocol follows IWG 2003 except: • Requires lower threshold of nucleated cell count of ≥100 • Absolute neutrophil count (ANC) ⩾1,000/μL • Auer rods and extramedullary disease not collected in EDC • Patient must be independent of RBC transfusion and platelet transfusion for a minimum of 1 week before each marrow assessment (Sievers et al 2001; Kantarjian et al 2012) **RECOMMENDATIONS:** -Medical adjudication - define rule for when cell count is not available, near 100 cells but not 100 cells, only biopsy is available (no aspirate) -Use ANC ⩾1,000/μL -Document in SAP auer rods and extramedullary disease is an investigator/hematopathologist assessment (not part of medical adjudication) -Medical adjudication for cases of CR or CR subtype but a RBC or platelet transfusion was recorded within 1 week

AML Response Assessment	IWG 2003 AML Response Criteria[1]	ELN 2017 AML Response Criteria[2]	Issues Requiring Clarification(s)	Study-specific Modification(s): ASTX727-02
	blood. A rare peripheral blood blast may be identified during regeneration. • Absolute neutrophil count (ANC) >1.0 × 10^9/L (1000/μL) • Platelet count ⩾100 × 10^9/L (100,000/μL)			
CR with incomplete blood count recovery (CRi)	All CR criteria except for residual neutropenia (ANC <1.0 × 10^9/L [1000/μL]) **OR** thrombocytopenia (platelet count <100 × 10^9 /L [100,000/μL])	All CR criteria except for residual neutropenia (ANC <1.0x10^9/L [1000/uL]) **OR** thrombocytopenia (platelet count <100x10^9/L [100,000/uL])	• CRi subjects did not meet CR criteria because either the ANC **OR** platelet count did not meet the CR threshold, but the other hematologic count did meet the CR threshold • Examples: ANC 1,200/μL and platelet 80,000/μL; or ANC 800/μL and platelet 120,000/μL	The protocol defines as "ANC <1,000/μL and no leukemic blasts" - criteria is incomplete in the protocol but available information is not incorrect • No platelet cell count definition • No transfusion independence definition • In the protocol, CRi is modified and defined as the non-CRp subtype of the original CRi IWG 2003 so subjects are not counted twice (Kantarjian et al, 2012) **RECOMMENDATIONS:** -Use as done in VIALE-A; CRi is collected; CRp is not collected.
CR with incomplete platelet recovery (CRp)			• CRp is not defined in IWG 2003 or ELN 2017; CRp was first defined by Sievers et al 2001 (as referenced in IWG 2003) as follows: CR except no platelet count recovery requirement (but meeting ANC requirement: ANC ≥1.0x10^9/L (1000/uL) • CRp is a subset of CRi (ie, overlaps, thus should not be additive in a composite response rate) • All CR criteria (including ANC criterion) except for residual thrombocytopenia (platelet<100 × 10^9 /L [100,000/μL]) • Example: ANC 1,200/μL and platelet 80,000/μL	• The protocol defines as a parallel assessment along with CRi, CRp is "ANC ⩾1000/μL, Platelets <100,000/μL, independence from RBC transfusions over the past week, no leukemic blasts" • In the protocol, CRi is modified and defined as the non-CRp subtype of the original CRi IWG 2003 so subjects are not counted twice (Kantarjian et al, 2012) **RECOMMENDATIONS:** -Approach like DACO-016, which reports CRp as a subset of CRi in final data table summary. Note that in Kantarjian et al, 2012 paper, the table is presented incorrectly. -CR+CRp composite are additive for an overall rate (Kantarjian et al, 2012 and Sievers et al, 2001)

AML Response Assessment	IWG 2003 AML Response Criteria[1]	ELN 2017 AML Response Criteria[2]	Issues Requiring Clarification(s)	Study-specific Modification(s): ASTX727-02
CR with partial hematologic recovery (CRh)			• CRh is not defined in IWG 2003 or ELN 2017 but can be used as an additional CR subtype that requires a lower threshold of ANC and platelet count recovery requirements (Kantarjian et al 2017) • All CR criteria (IWG 2003 or ELN 2017) except for residual neutropenia and/or thrombocytopenia; but meeting minimum ANC $\geq 0.5 \times 10^9$/L [500/μL]) **AND** platelet count $\geq 50 \times 10^9$ /L [50,000/μL]) • CRh should be assessed separately in those subjects not meeting CR by IWG 2003 or ELN 2017 criteria (independent of CRi or CRp)	• SAP defines CRh as a subset of CRi or CRp - this was transferred over from previous SGI-110 study. No pivotal studies have defined CRh as a subset of CRi or CRp because subjects may meet all 3 subtypes of CR, e.g., ANC 1200/μL and platelet 80,000/μL. **RECOMMENDATIONS:** -In the SAP, report using CRh as in Kantarjian et al 2017, which may be used as a composite (CR+CRh)
Partial remission (PR)	All of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate. A PR may also be assessed if the blasts are ≤ 5% but Auer rods are present.	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%	• For IWG 2003, Auer rods is a hematopathology determination and not easily collected in EDC	The protocol follows IWG 2003 except: • Auer rods are not evaluated for the alternative PR assessment
Treatment failure	Failure to achieve a CR in a Phase 3 trial or less than a PR in a Phase 1 or 2 trial. Resistant disease; Death due to complications from an aplastic or hypoplastic marrow; Indeterminate causes (death during first course of therapy); Morphologic relapse;	Primary refractory disease (no CR or CRi after 2 courses of intensive induction treatment); death in aplasia; death from indeterminate cause	• Treatment failure is not easily collected in EDC • Not assessed in most major studies (Appendix A and Appendix B)	• Not assessed in the protocol

AML Response Assessment	IWG 2003 AML Response Criteria[1]	ELN 2017 AML Response Criteria[2]	Issues Requiring Clarification(s)	Study-specific Modification(s): ASTX727-02
	Molecular or cytogenetic relapse			
Stable disease		Absence of CR_{MDR-}, CR, CRi, PR, MLFS; and criteria for progressive disease not met (period of SD should last for at least 3 months)	• SD time period requirement is not easily collected in EDC	• Not assessed for this study. Using no response (NR) to cover SD/PD as defined in Appendix C. **RECOMMENDATIONS:** -Medical adjudication SD/PD with available data including incomplete marrow/blood data and investigator assessment -NR=SD+PD+treatment failure
Progressive disease		Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: • >50% increase in marrow blasts over baseline (a minimum 15%-point increase is required in cases with <30% blasts at baseline); or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in ANC to an absolute level (>0.5 × 10^9/L [500/µL], and/or platelet count to >50 × 10^9/L [50,000/µL] nontransfused); or • >50% increase in peripheral blasts to ≥25 × 10^9/L (≥25,000/µL) (in the absence of differentiation syndrome or other clinical scenarios); or • New extramedullary disease	• PD assessed by ELN criteria but can also be based on clinical judgement or incomplete marrow or blood evidence of progressive disease, which may not be easily collected in EDC • ANC and platelet requirement is confusing and will be difficult to assess based on EDC data alone (was added to consider exception where blast increase can be seen in a regenerating marrow)	• Not assessed for this study. Using no response (NR) to cover SD/PD as defined in Appendix C. **RECOMMENDATIONS:** - Medical adjudication SD/PD with available data including incomplete marrow/blood data and investigator assessment -NR=SD+PD+treatment failure
Recurrence (IWG 2003) or Relapse (ELN 2017)	Morphologic relapse after attaining CR. Reappearance of leukemic blasts in the peripheral blood or ≥5% blasts in the marrow not attributable to any other cause. Appearance of new dysplastic changes should	• Hematologic relapse (after CR_{MDR-}, CR, CRi) defined as bone marrow blasts ≥5%; or reappearance of blasts in the blood; or development of extramedullary disease • Molecular relapse (after CR_{MDR-}) defined as if studied pretreatment, reoccurrence of MRD as assessed by RT-qPCR or by MFC	• Recurrent or relapse is not easily collected in EDC because it may require the incorporation of marrow and peripheral blood findings, and hematopathology and clinical determination	• In SAP, relapse defined as the earliest time point whereby BM assessment or PB assessment by the investigator indicate relapse/disease progression due to confirmed reappearance of leukemic blasts in PB or ⩾5% leukemic blasts in BM, or clinical progression determined by the investigator

AML Response Assessment	IWG 2003 AML Response Criteria[1]	ELN 2017 AML Response Criteria[2]	Issues Requiring Clarification(s)	Study-specific Modification(s): ASTX727-02
	also be considered relapse. In the setting of recent treatment, if there are no circulating blasts and the bone marrow blasts are 5-20%, a repeat marrow performed at least a week later is necessary to distinguish relapse from bone marrow regeneration. If recurrence is confirmed, the date of recurrence is defined as the first date that more than 5% blasts were observed in the marrow. Reappearance of extramedullary disease and molecular and/or genetic relapse is characterized by reappearance of the respective abnormalities.			• Auer rods and extramedullary disease not collected in EDC • Appearance of new dysplastic changes are not assessed well (hematopathologist assessment) or collected in EDC • Repeat marrow requirement in case of 5-20% blasts is not necessarily done as part of SOC

Footnotes:

[1] Cheson et al 2003 (IWG):

- **Early treatment assessment** is not included in this table and generally not included in response assessment tables. Per IWG 2003 criteria, evaluation is made ~7-10 days after completing the last dose of the initial course of treatment. This evaluation can be used in clinical trials and in clinical practice to obtain an early indication of antileukemic activity (e.g., day +14 marrow evaluation after 7+3 induction chemotherapy). May be incorporated in a study as an endpoint or in the treatment schema to guide therapy within the cycle.
- **Morphologic leukemia-free state (MLFS)** is not included in this table as a stand-alone response criteria but can on occasion be represented separately in a response assessment table if the objectives/endpoints of the study warrant reporting this response category which has no criteria for count recovery. See CR for definition of MLFS.
- **Three special categories of morphologic CR** should be considered: cytogenic CR (CRc), molecular complete remission (CRm), morphologic complete remission with incomplete blood count recovery (CRi). Refer to Cheson et al. for CRc and CRm criteria and recommendations.
- **Treatment failure criteria** - refer to Cheson et al. for details.

[2] Dohner et al 2017 (ELN):

- **CR without minimal residual disease (CR_{MRD-})** is not included in this table. If MRD is studied pretreatment, CR_{MRD-} is CR with negativity for a genetic marker by RT-qPCR, or CR with negativity by multiparameter flow cytometry (MFC). MRD evaluation may be incorporated in a study as an endpoint or in the treatment schema to guide therapy. If MRD is not evaluated in a study, CR is regardless of MRD status (positive, negative, or unknown). Refer to Dohner et al. for details.

AML Response Assessment	IWG 2003 AML Response Criteria[1]	ELN 2017 AML Response Criteria[2]	Issues Requiring Clarification(s)	Study-specific Modification(s): ASTX727-02
• **Morphologic leukemia-free state (MLFS)** is not included in this table as a stand-alone response criteria but can on occasion be represented separately in a response assessment table if the objectives/endpoints of the study warrant reporting this response category which has no criteria for count recovery. Per ELN 2017 criteria, requires bone marrow blasts <5%, absence of blasts with Auer rods, absence of extramedullary disease, and no hematologic recovery required. • Treatment failure criteria - refer to Dohner et al. for details.				

APPENDIX A: RECENT PIVOTAL STUDIES IN AML AND REPORTED RESPONSE CRITERIA

Study	Reported Response Criteria	Notes
Kantarjian et al 2012 (DACO-016, decitabine monotherapy)	CR CRi CRp Composite: CR+CRp PR SD PD	• Uses TI for 1 week • Composite rates are best response (each subject can only have 1 best response and individual rates add up to the composite rate)
DiNardo et al 2020 (VIALE-A, azacitidine+venetoclax)	CR CRi CRh PD CR by initiation of Cycle 2 Composite: CR+CRi best response but also rate by initiation of Cycle 2 Composite: CR+CRh	• Uses TI for 56 days between first and last day of treatment for this separate endpoint (definition is not part of CR determination) • Composite rates are best response (each subject can only have 1 best response and individual rates add up to the composite rate)
Wei et al 2020 (VIALE-C, cytarabine+venetoclax)	CR MRD CRi CRh PR Composite: CR+CRi Composite: CR+CRh Treatment Failure	• Follows IWG 2003 and ELN 2017 • CR has RBC TI (no period defined); CRi is considered regardless of RBC TI status (written as ±RBC transfusion independence) • Treatment failure was defined as failure to achieve MLFS or higher • Composite rates are best response (each subject can only have 1 best response and individual rates add up to the composite rate)
Kolitz et al 2020 (Vyxeos)	CR CRi Composite: CR+CRi	• Composite rates are best response (each subject can only have 1 best response and individual rates add up to the composite rate)
Dombret et al 2015 (azacitidine monotherapy)	CR CRi CRc-20 PR SD PD	• CRc-20 was defined as cytogenetic complete remission in at least 20 metaphases. • SD defined as anything except CR, CRi, disease progression, or treatment failure (early death).

Study	Reported Response Criteria	Notes
	Composite: CR+CRi	• Composite rates are best response (each subject can only have 1 best response and individual rates add up to the composite rate)

APPENDIX B: RECENT FDA DRUG APPROVALS IN AML AND REPORTED CR RATES IN PRESCRIBING INFORMATION

Study	Reported CR rates	Notes
Midostaurin	CR (no composite)	
Ivosidenib; IDH1i	CR Composite: CR+CRh	Composite rates are best response (each subject can only have 1 best response and individual rates add up to the composite rate)
Enasidenib; IDH2i	CR Composite: CR+CRh	Composite rates are best response (each subject can only have 1 best response and individual rates add up to the composite rate)
Vyxeos	CR (no composite)	
Gilteritinib	CR Composite: CR+CRh	Composite rates are best response (each subject can only have 1 best response and individual rates add up to the composite rate)
Venetoclax (for AML)	CR Composite: CR+CRh	Composite rates are best response (each subject can only have 1 best response and individual rates add up to the composite rate)

APPENDIX C: PROGRAMMING GUIDELINES

Table of response AML assessment tatus and programmable measures in ASTX727-02 study

Response Assessment Status	Programmable Measures*	Data not evaluable or not easy to capture in EDC (defer to hematopathologist and clinical investigator assessment; or sponsor medical adjudication)
CR	• Marrow blasts: <5% • ANC: ≥1000/µL • Platelets: ≥100,000/µL • No RBC and/or platelet transfusion within 7 days of BM evaluation • Peripheral blasts ≤1%[1]	• Auer rods[2] • Extramedullary disease[2] • Minimum 100 nucleated cell count from aspirate[3] • Flow data evaluating blast morphology[2] • Peripheral blasts present at low % (could be due to regeneration)[1] • CR criteria met but transfusion within 7 days of BM evaluation due to a medical situation[3] • Medical adjudication required when BM and CBC data not assessed on the same day[3]
CRi assess independently in all non-CR cases except progressive disease or relapse/recurrence	• Marrow blasts: <5% • ANC: ≥1000/µL **OR** Platelets: ≥100,000/µL • Transfusion: no RBC and/or platelet transfusion within 7 days of BM evaluation • Peripheral blasts ≤1%[1]	• Auer rods[2] • Extramedullary disease[2] • Minimum 100 nucleated cell count from aspirate[3] • Flow data evaluating blast morphology[2] • Peripheral blasts present at low % (could be due to regeneration)[1] • CRi criteria met but transfusion within 7 days of BM evaluation due to a medical situation[3] • Medical adjudication required when BM and CBC data not assessed on the same day[3]
CRp assess independently in all non-CR cases except progressive disease or relapse/recurrence	• Marrow blasts: <5% • ANC: ≥1000/µL • Platelets: any platelet count <100 • Transfusion: no RBC transfusions within 7 days of BM evaluation (no platelet recovery needed so this is independent of platelet transfusion status) • Peripheral blasts ≤1%[1]	• Auer rods[2] • Extramedullary disease[2] • Minimum 100 nucleated cell count from aspirate[3] • Flow data evaluating blast morphology[2] • Peripheral blasts present at low % (could be due to regeneration)[1] • CRp criteria met but transfusion within 7 days of BM evaluation due to a medical situation[3] • Medical adjudication required when BM and CBC data not assessed on the same day[3]
CRh	• Marrow blasts: <5%	• Auer rods[2]

Response Assessment Status	Programmable Measures*	Data not evaluable or not easy to capture in EDC (defer to hematopathologist and clinical investigator assessment; or sponsor medical adjudication)
assess independently in all non-CR cases except progressive disease or relapse/recurrence	• ANC: ≥500/μL • Platelets: ≥50,000/μL • Transfusion: no RBC and/or platelet transfusions within 7 days of BM evaluation • Peripheral blasts ≤1%[1]	• Extramedullary disease[2] • Minimum 100 nucleated cell count from aspirate[3] • Flow data evaluating blast morphology[2] • Peripheral blasts present at low % (could be due to regeneration)[1] • CRp criteria met but transfusion within 7 days of BM evaluation due to a medical situation[3] • Medical adjudication required when BM and CBC data not assessed on the same day[3]
PR	• Marrow blasts: ≥50% reduction of blast % from baseline but blast count within 5-25% (inclusive of 5% and 25% • ANC: ≥1000/μL • Platelets: ≥100,000/μL • Transfusion: no RBC and/or platelet transfusions within 7 days of BM evaluation • Peripheral blasts ≤1%[1]	• Auer rods[2] • Extramedullary disease[2] • Minimum 100 nucleated cell count from aspirate[3] • Flow data evaluating blast morphology[2] • Peripheral blasts present at low % (could be due to regeneration)[1] • PR criteria met but transfusion within 7 days of BM evaluation due to a medical situation[3] • Medical adjudication required when BM and CBC data not assessed on the same day[3]
SD	• Progression: no progression • Response: absence of CR, CR subtype, PR, PD • Duration: lasting ≥3 months • Recurrence/relapse: absent	• Auer rods[2] • Extramedullary disease[2] • Minimum 100 nucleated cell count from aspirate[3] • Medical adjudication required when BM and CBC data not assessed on the same day[3]
PD	• Marrow blasts: >50% increase in marrow blast % from baseline (a minimum 15% increase in cases with <30% marrow blasts at baseline); or >70% marrow blasts over at least 3 months; or >50% increase in peripheral blasts to ≥25 x 10^9/L (≥25,000/μL) • Response: absence of CR, CR subtype, PR, SD • Presence of recurrence/relapse	• Auer rods[2] • Extramedullary disease[2] • Minimum 100 nucleated cell count from aspirate[3] • Clinical or symptomatic progression (or incomplete data) accepted for PD response assessment • Medical adjudication required when BM and CBC data not assessed on the same day[3]

Response Assessment Status	Programmable Measures*	Data not evaluable or not easy to capture in EDC (defer to hematopathologist and clinical investigator assessment; or sponsor medical adjudication)
	• Regardless of ANC, platelets, transfusions[4]	
NR not a published criteria	• Response: defined as absence of CR, CRi CRp, CRh, PR (when SD and PD are not assessed)	• Used in place of SD/PD as needed
Recurrence (IWG 2003) or Relapse (ELN 2017)	• Response: CR or CR subtype achieved • Marrow blasts: ≥5% marrow blasts not attributable to any other cause after CR achieved and sustained on repeat assessment (to distinguish relapse from regeneration)	• Auer rods[2] • Extramedullary disease[2] • Minimum 100 nucleated cell count from aspirate[3] • Frank dysplasia not collected in EDC[3] • Marrow blasts ≥5% not attributable to any other cause[2] • Medical adjudication required when BM and CBC data not assessed on the same day[3] • Clinical or symptomatic progression (or incomplete data) accepted for recurrence or relapse assessment

[1]The threshold for the purpose of programming was not defined in IWG 2003 and not mentioned in ELN 2017. Requires medical adjudication if present but for programming chose ≤1%.
[2]Data not collected. SAP should state that this data is presumed evaluated/assessed by hematopathologist and clinical investigator as routine part of assessment.
[3]Refer to Appendix D for guidelines for medical adjudication.
[4]The ELN 2017 criteria mentions "without at least a 100% improvement" in ANC or platelet count - this is difficult to capture in the EDC or evaluate by programming. Omitted this detail in the table since AML is not an indolent disease and progressive disease tends to be obvious with other supportive laboratory and clinical data.

*ANC values should extend to thousandths digit (e.g., **ANC 0.250** x10^9/L = 250/uL); Platelet count values should extend to hundreds digit (e.g., **Platelet 120** x10^9/L = 120,000/uL). Edit checks/site queries are needed especially if ANC hovers around 1000 or 500/uL and platelet hovers around 100,000/uL and 50,000/uL, i.e., where the thresholds for CR and CR subtypes are defined. For example, a reported or derived ANC of "0.5" may be 0.499 or 0.505 and this would affect CR assessment (see CRh criterion).

APPENDIX D: MEDICAL ADJUDICATION RULES ASTX727-02 STUDY

This is a working document and may require updating from time to time.

1. **100 nucleated cells requirement**
    a. EDC was not designed correctly to capture whether >100 nucleated cells were evaluated on aspirate
        i. Solution - in EDC, it was asked was the aspirate "sample adequate"?
            1. If yes, use data as quantified by hematopathologist
            2. If answer is blank or "sample not adequate" then options are:
                a. Try to obtain redacted hematopathology report, or
                b. If not possible, send investigator a form that requires them to indicate that the BM evaluation was overall adequate for response assessment (e.g., tissue biopsy was used to evaluate blast count and response assessment). File an administrative letter or as appropriate.
2. **Peripheral blasts**
    a. If ≤1% and other CR/CR subtype criteria met, can assume part of regenerating marrow process
    b. If >1% and other CR/CR subtype criteria met, use at least one follow-up CBC with differentials to confirm CR/CR subtype criteria (blasts should lessen over days and become ≤1%)
3. Transfusions within 1 week of a CR or CR subtype (expecting to be a rare occurrence)
    a. If CR/CR subtype criteria met and there is a documented RBC or platelet transfusion within 1 week, consider clinical circumstances of the transfusion - reviewing EDC (AEs, medical hx, concomitant procedures) or asking investigator for details (document and file an administrative letter or as appropriate). This will cover the rare circumstance when the subjects are transfused electively for a medical history, AE, or procedure.
4. **BM/CBC not on same day (priority of evaluation order)**
    a. Evaluate response using BM biopsy and CBC with differential from the same day
    b. If not matched, look for the closest CBC (usually should be ±1 week); assess response using the combination of data and use the later of the two dates as first response
    c. If a marrow is done and a CBC >1 week later shows additional count recovery and meets a new response, enter response at date when CBC data shows criteria met (ask sites to enter any interim missing weekly labs)
    d. If two CBCs are done with the same # days from the marrow and show the same response, use the marrow date for response assessment; if one CBC shows a better response use that CBC and use the date of that CBC
    e. If two CBCs are done with the same # days (±) from the marrow and show the same response, use the marrow date for response assessment; if the later CBC shows a better response use that CBC date; if the earlier CBC shows a better response, use the BM biopsy date
    f. Note: since CBC with differential on a weekly basis may be critical for proper dating of changes in response assessment (e.g., subject with SD and progressing towards a CR), ask sites to add weekly labs even if local labs (pass to DM to query for all missing weekly labs)
5. **No interim BM and CR is achieved on a later CBC**

a. If MLFS (morphologic leukemia-free state), can assess a CR or CR subtype based on a later CBC with diff showing count recovery to meet criteria
b. If CR subtype (includes MLFS), can assess a CR based on a later CBC with diff showing count recovery to meet criteria
c. If PR (blasts 5-20%) or SD, cannot assess a higher response category based on a later CBC with diff without a BM evaluation

6. Bone Marrow Blasts Percentages
   a. If BM ≥5% is not seen on laboratory values at screening, to be evaluable, there must be evidence in the EDC supporting the AML diagnosis (BM ≥5%). To rule out the possibility this is a protocol violation (patient does not have a diagnosis of AML), documentation of either 1) any pre-screening maneuvers that reduced blasts (eg hydroxyurea or single dose of cytarabine or mitoxantrone) or 2) the subject has peripheral blasts >20% but not marrow blasts >20%, or 3) the subject presents as a myeloid sarcoma which is a type of AML that grows as a tumor and may have a marrow that does not reach AML blast count or is even completely normal. If there is a bone marrow before the screening marrow that documents the AML before #1, ask the site to add the data as an unscheduled BM and date it accordingly for proper documentation and verification of the AML diagnosis. These are the typical circumstances when subjects with AML have blasts <20% at baseline.
   b. BM blasts fall from above to below 5% then return above and below 5% again. This may be due to BM rejuvenation. Requires medical adjudication to determine if still in best response or relapsing. Answer to this should be apparent over time.

APPENDIX E: STANDARD BDM TABLE OUTPUTS OF RESPONSE ASSESSMENT

(1) using 2003 IWG and Kantarjian et al 2017

Taking ASTX727-02 AML as a sample:

ASTX727-02 EMEA AML Submission
Population: Efficacy Analysis Set

Table xx.x.x
Analysis of Overall Response

	Sequence A (N=xx)		Sequence B (N=xx)		Total (N=xx)	
	n (%)	95% CI	n (%)	95% CI	n(%)	95% CI
Best Response [1]						
CR	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
CRi	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
CRp	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
PR	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
SD	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
PD	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
NE	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Composite Response Rates						
CR + CRi	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
CR + CRi + PR	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
CR + CRp	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
CR + CRh	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
CRh[2]	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)

The 95% CI is Clopper-Pearson confidence interval.
CR=complete response; CRp=complete response with incomplete platelet recovery; CRi=CR with incomplete blood count recovery; PR=partial response; SD = Stable Disease; PD = Progressive Disease; NE=Not evaluable. Subjects who did not have a valid post-treatment efficacy assessment (ie, no post-treatment BM/PB sample or the quality of BM/PB sample is not adequate for an assessment of efficacy) were classified as NE for response classifications.
(1) Modified 2003 IWG response criteria (Cheson et al. 2003) and DACO-016 CSR was used for CR, CRi, CRp, PR, SD, and PD, and NE.
(2) Kantarjian et al 2017 was used for the CRh assessment.
Sequence A: ASTX727 in Cycle 1; IV decitabine in Cycle 2. Sequence B: IV decitabine in Cycle 1; ASTX727 in Cycle 2.

Program Location: m:\astx727\02\biostat\phase3_eu\devel\program\tables\t_response1.sas, Data Cut Off: 04JUN2021, Database Extracted: 16JUL2021
Output: t_14.3.1_response1.rtf (Date Generated: 01SEP2021:13:56), Source Data: ADAMDATA.ADSL, ADRS

(2)) using 2017 ELN and Kantarjian et al 2017

<Protocol>
Population: <Analysis Set>

Table xx.x.x
Analysis of Overall Response

	Group 1 (N=xx)		... (N=xx)		Total (N=xx)	
	n (%)	95% CI	n (%)	95% CI	n(%)	95% CI
Best Response [1]						
CR	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
CRi	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
PR	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
SD	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
PD	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
NE	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Composite Response Rates						
CR + CRi	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
CR + CRi + PR	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
CR + CRh	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
CRh[2]	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)

CR=complete response; CRi=CR with incomplete blood count recovery; PR=partial response; SD = Stable Disease; PD = Progressive Disease;
NE=Not evaluable. Subjects who did not have a valid post-treatment efficacy assessment (ie, no post-treatment BM/PB sample or the quality of BM/PB sample is not adequate for an assessment of efficacy) were classified as NE for response classifications.
(1) ELN 2017 AML Response Criteria.
(2) Kantarjian et al 2017 was used for the CRh assessment.
Group 1: ....
Program Location: m:\...\devel\program\tables\t_xxx.sas, Data Cut Off: DDMMYYYY, Database Extracted: DDMMYYYY
Output: t_xx.x.x_xxxx.rtf (Date Generated: DDMMYYYY:HH:MM), Source Data: ADAMDATA.ADSL, ADRS

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8.2 Appendix 2: Summary of Changes

Rationale for Version 2.0

Version 2.0 is an update to the AML Response Assessment Criteria.

Summary of Changes:

1) Section 3.2.2 The reference for CRp (Kantarjian et al 2012) is added; " complete response with partial hematologic recovery (CRh) will also be assessed as a subset of CRi or CRp" is removed.

2) Table 2: The criteria for CRi are changed to be consistent with IWG 2003 AML Response Criteria (Cheson et al 2003) instead of the protocol.

3) Section 7.5.1: Progressive disease and stable disease are added based on the European LeukemiaNet (Döhner et al 2017).

4) Section 7.5.2: Changing CRp, CRi to CRi (or CRp) due to that CRp is the subset of CRi

5) Section 7.5.3: Duration of CR or CRp is added based on DACO-016 (Kantarjian et al 2012).

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